CURRENT THEORETICAL METHODS APPLIED TO STUDY CYCLODEXTRINS AND THEIR COMPLEXES

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Abstract

This review deals with the description of current theoretical methods tostudy chemical and physical chemistry properties of cyclodextrins and their complexes. This study covers from 1998 to present, with the exception of some papers not included in a rather recent review. Five thematic areas were chosen to organize the information: computational studies of host-guest compounds, computational studies for interpreting spectral data, free energy simulations, enantiomers separation, and quantitative structure-activity (property) relationships.

Resumen

Esta reseña trata acerca de la descripción de los métodos teóricos usados actualmente en el estudio de propiedades químicas y físicas de las ciclodextrinas y de sus complejos. La revisión abarca desde 1998 hasta el presente, a excepción de algunas publicaciones que no fueron incluidas en una reseña bastante reciente. Se eligieron cinco áreas temáticas para organizar la información: estudios computacionales de compuestos huésped-anfitrión, estudios computacionales para la interpretación de datos espectroscópicos, simulaciones de energía libre, separación de enantiómeros, y relaciones cuantitativas de estructura-actividad.

Introduction

Cyclodextrins (CDs) are cyclic oligomers of α-D-glucose formed by the action of the glucosyltransferase enzyme on starch. Three CDs are readily available: αCD, having six glucose units; β-CD, having seven glucose units; and γ-CD, having eight glucose units. CDs with fewer than six glucose residues are too strained to exist, whereas those with more than eight residues are very soluble, rather difficult to isolate, and hardly studied to date. α-CD, β-CD and γ-CD are commonly referred to as the native CDs. Very many covalently modified CDs have been prepared from the native forms. Figures 1-3 show the chemical structures of α-CD, β-CD, and γ-CD, respectively.

The glucose units are connected through α-1,4 chemical bonds, as shown in Figure 4.

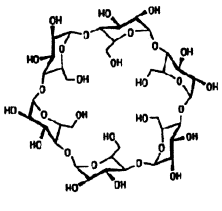


Figure 1

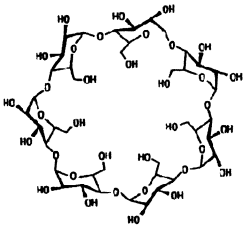


Figure 2

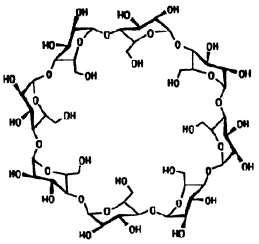


Figure 3

The structural consequence of this bonding feature is the formation of a doughnut-shaped molecule having, for *n* glucose residues, one rim lined with *n* primary hydroxyl groups, the other rim lined with 2*n* secondary hydroxyl groups, and the interior of the cavity lined with, from the secondary hydroxyl rim inwards, a row of CH groups (*i.e.* the C-3 carbon atoms), then a row of glycosidic oxygen atoms, and then a row of C-5 CH groups. CDs are often described as having a torus geometry, but it is somewhat realistically pictured as a shallow truncated cone, the primary hydroxyl rim of the cavity opening having a rather reduced diameter compared with the secondary hydroxy rim. Besides, in some cases the torus may depart significantly from perfect symmetry.

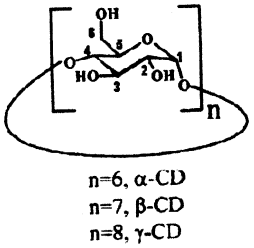


Figure 4

The possession of this peculiar cavity makes the CDs attractive subject for study. The CD exterior area, bristling with hydroxyl groups, is fairly polar, whereas the interior of the cavity is nonpolar relative to the exterior and relative to the usual external environments. These compounds have therefore been studied as "hosts" for "guest" molecules capable of entering (completely or partially) the cavity and thus forming noncovalent host-guest inclusion or occlusion complexes. The non-bonding electron pairs of the glycosidic oxygen bridges are directed towards the inside of the cavity, producing a high electron density and lending it some Lewis-base character. Figure 5 illustrates the characteristic structural features of CDs.

CDs' chemistry has been reviewed many times through book-length treatments [1-6] and several shorter and more specialized articles [7-27]. There exist a significant

number of computational studies over the past fifteen years that have led to a deeper understanding of the structure, dynamics and chemical behavior of CDs. Two excellent review articles covering theoretical aspects of CDs and their inclusion-occlusion complexes have been published [28, 29]. The last article covers up to 1998, and since then a meaningful number of computational studies have appeared further describing the detailed, atomic level behavior of these molecules.

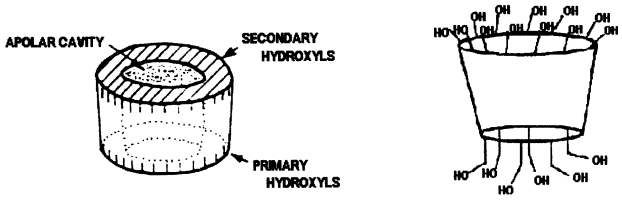


Figure 5

The approximate dimensions of CDs are shown schematically in Figure 6.

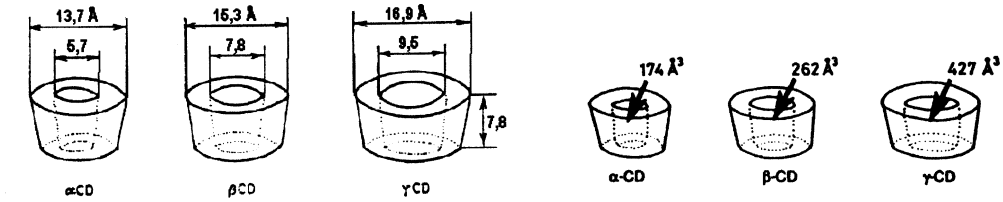


Figure 6

This review deals with computational studies presented since 1998. Since we had published previously the theoretical chemistry methods currently employed to study CDs and their inclusion-occlusion complexes [27], we omit such description. Besides, other rather recent publications have also included good enough information details [28, 29] on this point.

We have organized the presentation of the information into five main areas. Naturally, these areas are not necessarily mutually exclusive, but they tried to be representative of the most important issues related to CDs research field. These thematic areas are: a) Computational studies of host-guest complexes, b) Computational studies for interpreting spectral data, c) Free energy simulations, d) Enantiomers separation, and e) Quantitative structure activity (property) relationships.

Since some significant papers published before 1998 were not included in those recent compilations [28, 29], we deem suitable to insert them in this review.

Computational studies on host-guest complexes

In the last five years there has been an increase in research involving CDs, given that their ability to form complexes with a variety of compounds makes them particularly useful for catalysis [30] and chiral separation [31, 32]. The decisive factor for the inclusion complexes is that the guest molecule should fit into the cavity, the driving force

being more or less independent of the nature of the guest molecule [2]. Nevertheless, geometry is not the sole factor determining the stability of a complex since experimental results show that some molecules are well compatible with α-CD and they have no satisfactory fitting in larger cavities [2, 32]. Complex formation also depends on the polarity of the guest molecule, which is oriented in the CD in such position as to achieve maximum contact between the hydrophobic part of the guest molecule and the internal surface of the CD cavity. The hydrophilic part of the guest molecule remains, as far as possible, on the outer surface of the complex. However, it is generally believed that the van der Waals interaction acts as the main driving force for the interaction between CDs and guest compounds [2]. This assumption is fully supported by numerous molecular mechanics calculations performed on α- and β-CD with one guest molecule [33-38]. However, these studies focused on structural and energetic properties of inclusion complexes of CDs with one specific type of guest molecule (*i.e.* alcohols, esters, amines, etc.), which do not allow a generalization for molecules with different shapes or/and sizes. Alvira [39] addressed this point presenting a simple model and calculation method for the evaluation of the physisorption energy of molecules with different sizes in any CD, irrespective of their composition. This study is closely related to other significant contributions on adsorption performed in cavities with different geometries [40 - 46], mainly cylindrical and spherical. The interaction energy between the guest molecule and the CD was modeled by a sum of pairwise Lennard-Jones (6,12) potentials and a continuum description of the cavity walls was used, assuming two types of geometries for the latter: cylindrical and conical. This simple interaction potential allowed the author to establish the σ parameter (distance parameter in the Lennard-Jones potential) of the guest molecule forming the most stable inclusion complex with each CD, as well as the maximum size of the guest molecule above which inclusion complexes cannot be formed.

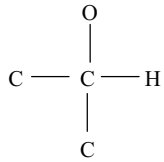
Bodor *et al* performed a series of semiempirical molecular orbital (MO) calculations using the AM1 method on the inclusion complexes of α- and β-CD with benzoic acid and phenol in the "head-first" and "tail-first" positions [47]. The AM1 results showed that α-CD complexes with both guest compounds in the "head-first" positions are more stable than the "tail-first" position, while the β-CD complex with phenol in the "tail-first" position is more stable, but with benzoic acid, the "head-first" position is more stable. The driving forces for complex formation were investigated based on different intramolecular and intermolecular interactions, such as steric fit, dipole-dipole interaction, intramolecular hydrogen bonding, intermolecular hydrogen bonding, and the enthalpies of formation of host and guest molecules calculated at their geometries in the complex and at their optimized geometries. In addition, AM1 calculations were performed on the β-CD complexes with benzoic acid in the "tail-first" and "head-first" positions with the benzoic acid moved stepwise along the Z-axis of the β-CD principal axis coordinate system.

Manunza *et al* investigated the interaction between four cycloprothrin derivatives and β-CD by means of molecular dynamics (MD) [48]. Several *in vacuo* trajectories were calculated for each system imposing a 1:1 stoichiometry. Moreover, for one particular guest-host couple, the 1:2 guest-host ratio was analyzed. They also took into account the influence of the solvent and of the temperature. The adduct formation

involves the phenyl groups of the guest molecules which mainly interact with the hydrophobic cavity of the host by van der Waals forces. The MD experiments were performed employing the DLPOLY2 program [49]. The AMBER plus OLYCAM [50] force field was used with the adequate adaptations. The partial atomic charges were fitted to the electrostatic potential computed by *ab initio* GAMESS calculations performed at the 6-31G basis set level accuracy on a fragment formed by 3 glucopyranose units. A relative dielectric constant value of 1.0 was employed in all the simulations.

Poly[(R)-hydrxybutanoate] (P(3HB)) is an active biopolyester synthesized as a storage material for carbon and energy in several prokaryotic microorganisms. Since its discovery, P(3HB) and related poly[(R)-3-hydroxyalkanoates] have attracted remarkable interest both in basic research and industrial applications due to their biodegradability and biocompatibility which permit them to be employed as suitable biodegradable substitutes for conventional plastic materials. Li *et al* reported experimental results on NMR studies on complex formation between 3HB and d3HB and α-CD, β-CD, and γ-CD and they found that only d3HB selectively forms inclusion complexes with β-CD with a 1:1 stoichiometry [51]. Although the authors have discussed some main contributions to the driving forces for the complex formation on the basis of the results of thermodynamic analysis, they were not conclusive due to the information source. This led Castro and Jubert [52] to resort to Molecular Mechanics (MM) method to study theoretically these complexes. All calculations for 3HB, d3HB, α-CD, β-CD, γ-CD and the whole set of possible host-guest complexes were performed using the MM+ [53] force field implemented in the HyperChem® package. Molecular Modeling results were in agreement with experimental findings, predicting the complex formed d3HB with β-CD is the most stable one.

Steiner *et al* presented the results of quantum chemical calculations on the weak polar host-guest interactions in crystalline cyclomaltoheptose (β-CD)-but-2-yne-1,4-diol heptahydrate (A). This study was motivated by the fact that if polar guest molecules are included in the CDs' cavities, they have limited opportunity to satisfy their hydrogen bond potentials. Typically, guest molecules carrying hydroxyl groups are oriented in such a way that hydrogen bonds can be formed through the cavity openings to neighboring CD or crystal water molecules. Hydrogen bonds can also be formed with the primary O-6 hydroxyl groups which are placed at the narrower of the two cavity openings The interglycosidic O-4 atoms are sterically poorly accessible, and serve only occasionally as acceptors of O-H...O hydrogen bonds [54,55]. O/N-H...O hydrogen bonds with either hydroxyl groups or O-4 atoms are often regarded as the only possible host-guest hydrogen bonds in CD inclusion complexes. However, the authors found structural evidence for C-H...O hydrogen bonding [56-59], and also for directional C-H...π interactions [57] in a number of CD inclusion complexes. The typical energies of C-H...O and C-H...π hydrogen bonds depend on the nature of the C-H donor. For the very weakly polarized methyl donors, C-H...O bond energies are around 0.5 kcal/mol, not much above the energies of van der Waals interactions. For strongly polarized C-H groups like in chloroform or in terminal alkynes, C-H...O energies may be larger than 2 kcal/mol [60]. For the other types of C-H donors, hydrogen bond energies are in between these extremes. The C-H groups forming the surface of CDs cavities, C-3-H and C-5-H, are of a significantly activated type:



For this kind of donor, C-H...X interactions have not yet been the subject of theoretical investigations. In order to get an impression of the energy contribution of weak hydrogen bonds in the stabilization of CD inclusion complexes, Steiner *et al* performed the calculations on this particular structure. They found that calculated bond energies for the weak polar interactions in the crystal packing of (β-CD)-but-2-yne-1,4-diol heptahydrate are low with numeric values in the range 0.7 to 1.1 kcal/mol. This is roughly around a quarter of O-H...O hydrogen bonds in carbohydrates, but clearly above the dispersion energies. They concluded that arrangements involving weak hydrogen bonds are more prone to disorder than those stabilized by conventional hydrogen bonds: the entropy gain due to disorder can easily exceed the enthalpy loss due to breaking the weak hydrogen bonds.

Aicart *et al* published potentiometric and molecular modeling studies on molecular encapsulation of flurbiprophen and/or ibuprophen by hydroxypropyl-βCD in aqueous solution [61]. In fact, thermodynamic and structural studies of the binding of the non-steroidal anti-inflammatory drugs, flurbiprophen and ibuprophen, to hydroxypropyl β-CD (HPBCD) have been carried out from pH potentiometric measurements, MM, and MD calculations. The potentiometric study was performed by measuring the pH of aqueous solutions of the drugs as a function of CD concentration, at several temperatures ranging from 15 to 40°C. The dissociation constants of the drugs, as well as the binding constants of the inclusion complexes formed by HPBCD and the ionized and nonionized drugs, have been simultaneously determined at all the temperatures within the range. The nonionic forms have shown a higher affinity to HPBCD than their ionic counterparts. A van't Hoff analysis of the determined binding constants revealed that the complexes formed by the flurbiprophen species and HPBCD are enthalpy driven, with a favorable enthalpic term and an unfavorable entropic term. Both contributions were found to be temperature independent (*i.e.* $\Delta C_p°=0$). However, in the case of ibuprophen, a dependence of the thermodynamic quantities $\Delta H°$ and $\Delta S°$ with temperature has been found. Thus, these association processes change from entropy driven at $T \leq 25°C$ to enthalpy driven at $T > 25°C$, which is due to a negative $\Delta C_p°$ value, typically found in biological associations where hydrogen-bonding interactions are present. MM and MD calculations were used to obtain structural and dynamics information of the free ligands, the receptor, and the four inclusion complexes. Flurbiprophen acid has been found to enter the HPBCD cavity leaving the carboxylic group upward, while the energetically favored inclusion of flurbiprophenate, ibuprophen acid, and ibuprophenate leaves the carboxylate or carboxylic group downward. In either case, the van der Waals contacts between the phenyl ring of the ligand and a lipophilic zone of the CD cavity, the entropy factor, and possible intermolecular hydrogen bonding were shown as the main responsible of the stability of the inclusion complexes. The estimation of the conformational stability of the free and associated ligands confirmed that the carboxylic

species of flurbiprophen and ibuprophen are encapsulated with a higher stability than that of their counterparts, in agreement with the potentiometric results.

The modeling of the free ligand species present in the equilibrium, that is, flurbiprophen (HFLUR) and ibuprophen (HIBU) acids, flurbiprophenate ($FLUR^-$) and ibuprophenate (IBU^-) anions, the free receptor HPBCD, and also the different complexes ligand:receptor were performed using mixed mode Monte Carlo/Stochastic Dynamics (MC/SD) [62] as implemented in Macromodel V4.5 [63]. The previous step implies the generation of a starting minimized structure. In all the simulations the force field used was MM3 [64], with the continuous water solvation model GB/SA [65]. The temperature was maintained constant to 300 K by coupling the system to a thermal bath. The time step was 1 fs. The analysis of the MC/SD simulations and the experimental data allowed the authors to state that several intermolecular forces can drive the association process, such as van der Waals and hydrogen bond interactions, and in the case of flurbiprophen also the F...HO interaction. The F...HO interaction seems to be theoretically and experimentally less important than the other two, as deduced by the higher stability of the HIBU complex with respect to the HFLUR complex. The modeling also offers an explanation for the lower stability observed for the ionized complexes. In these complexes, the ligand disposes on average out of the CD cavity thus reducing the possibilities to establish van der Waals and hydrogen bond interactions with the receptor.

Pozuelo *et al* performed MD simulations *in vacuo* on "channel type" polyrotaxanes composed of β-CDs threaded onto isotactic and syndiotactic poly(propylene glycol) (PPG) [66]. In the most stable complex, the β-CDs form a closed-packed structure from one end of the PPG chain to the other. Non-bonded van der Waals interactions between β-CD and PPG are the main source of stabilization of the complex. Head-to-head and tail-to-tail orientation of successive β-CDs in the complex is more favorable than a head-to-tail orientation, due to the intermolecular hydrogen bonding between head-to-head β-CDs units. β-CDs in polyrotaxanes adopt a more rigid and symmetrical macro-ring conformation than an isolated β-CD does. Formation of the polyrotaxane is accompanied by an increase in the number of *trans* states at the bonds in the backbone of PPG. For this reason, the PPG chain in the polyrotaxane is much more extended than the unperturbed chain. MD simulations had been used to study the conformations and mobility of similar systems in which a polymer is confined to a narrow channel [67-72] including MD simulations [73] of complexes of α-CD with end-capped PEG of the kind described by Harada [74], favoring 2.6 (±0.1) oxyethylene units per CD. The α-CDs in the complex formed a close-packed structure from one end of the PEG chain to the other end. The van der Waals non-bonded interactions provide the main source of stability for the complex. Hydrogen bonds favor slightly head-to-head, tail-to-tail sequences of α-CDs. The α-CD in the complex is more symmetric than the isolated α-CD, and the PEG in the complex is more extended than the unperturbed chain. The MD trajectories in this work were computed using SYBYL 6.3 from Tripos Associates (St. Louis, Missouri) and the Tripos Force Field 5.2 [75]. The contribution to the energy from the hydrogen bonds was incorporated in the van der Waals and coulombic terms. All simulations were performed *in vacuo*, rather than in aqueous solution. The molecules studied were isolated chains of the isotactic poly-((R)-propylene glycol) and the syndiotactic poly((RS)-propylene glycol) containing ten monomer units and the

complexes of these chains with β-CD. Analysis of the MD simulations *in vacuo* for PPG suggests for β-CD polyrotaxanes a composition of about 2.5 monomer units per CD, with β-CDs separated by approximately 8 A, forming a close-packed structure from one end to the other. β-CDs in polyrotaxanes have a cylindrical shape, and they are less distorted than the isolated β-CD. Their macro-rings are more symmetric and less flexible in the complex than in the isolated β-CD. However, the tails and heads, which define the entrance into the cavity of the β-CD in the complex, have flexibility similar to that seen in the isolated β-CD. A twist around the *trans* states at the bonds to the bridging oxygen atoms is observed for β-CDs in the complex, and the *cis* state is totally suppressed. The *trans* states are strongly preferred at all internal bonds of the PPG chains in the complex, causing them to become much more extended than in the unperturbed state. The calculated binding energy suggests that complexes formed with isotactic PPG chains are slightly more stable than those formed with syndiotactic ones.

Binding of 1,4-di-R-bicyclo[2.2.2]octanes [R = OH (bic), Me (bim)] to α-CD, β-CD and γ-CD in the gas phase and in aqueous solution have been studied by Stödeman *et al* [76] via force-field computations and isothermal titration microcalorimetry, respectively. For bic, a 1:1 stoichiometric model was assumed in the treatment of the microcalorimetric data. In the gas phase, for both α-CD and β-CD, bim penetrates less deeply into the cavity than bic. The shallow penetration of bim allows a second α-CD to bind, in agreement with the 1:2 complex observed in a solvent mixture by NMR measurements, as reported earlier. In aqueous solution, β-CD binds to bic with moderate Gibbs energy change, a large and negative heat capacity change and compensating temperature dependences for the enthalpy and the entropy changes.α-CD and γ-CD bind weakly to bic in solution, whilst large binding energies were obtained for both guests for the gas-phase interactions with α-CD and β-CD.

Force field analysis of the 1:1 complexes of α-CD and β-CD with bic and bim was carried out using the MM2(91) force field [77] implemented in the MacMimic program package [78,79]. The search for minimum-energy geometries was performed starting from various input geometries. The minimum-energy structures were obtained after relaxation of all degrees of freedom. The extent of penetration was explored by allowing the following constraints. The center of the cavity was defined as the geometrical center of all glycosidic oxygen atoms. The distance from this point to the midpoint between the bridgehead carbon atoms of the guest drove the penetration. This distance was the only constrained parameter in the calculations. The computations were carried out without inclusion of water or other solvent molecules. Electrostatic interactions were calculated using the standard routine with a relative permittivity of 1.5. The enthalpy of complexation was estimated as the difference between the calculated energies of the complex and the sum of the CD and the guest molecules. The authors concluded that binding affinities between CDs and 1,4-bicyclo[2.2.2]octanes, and other guest molecules result from a subtle interplay between steric conditions, the hydration of the free species and the complexes, van der Waals interactions, dipole-dipole interactions, hydrogen bonding, and conformational changes of the CD molecules.

Modified CDs, which have an appending moiety, form various conformations depending of its moiety. Usui *et al* have examined the factors that determine the

conformation of modified CDs with *p*-dimethylaminobenzoyl and *p*-nitrobenzoyl moiety as pendant (DMAB-β-CD and NB-β-CD, respectively), using computational chemistry [80]. The structures and potential energies were calculated using MD conformational search, and the relationship between conformation and energy calculated from force field was investigated. These calculations suggested that the conformation of the modified CDs is dominated by the opposing influences of the van der Waals energy, which favors locating the appending moiety inside the CD cavity, and the angle related to the bending energy, which favors the moiety outside the cavity.

Model building of the initial starting conformations of DMAB-β-CD and NB-β-CD was performed with the aid of interactive molecular graphics. Two types of initial conformations were prepared for each of DMAB-β-CD and NB-β-CD. The first one is the conformation with the appending moiety included in its CD cavity (form A) and the second one is that with the appending moiety located outside the CD cavity (form B). In order to obtain the partial atomic charges for appending moieties the AM1 hamiltonian [81] of Ampac version 2.10 was used. The charges for the CD ring were obtained from parametrized sets with consistent valence force field (CVFF) [82]. All parameters were used as implemented in the generic parameter set of CVFF. The programs InsightII ver. 2.20 and Discover ver. 2.90 from Biosym, Inc., were used for model building and MD calculations. Theoretical analysis reveals that the self-inclusion structure of DMAB-β-CD is stabilized by van der Waals interaction between the appending moiety and the CD ring in spite of the destabilization by the distortion of the CD ring. On the other hand, in the case of NB-β-CD, the stabilization by van der Waals interaction is invalidated by the destabilization of the distortion in the CD frameworks. These results are in agreement with the experimental results and demonstrate that the MD conformational search is useful for explaining the experimentally determined structures as well as for predicting the conformations of modified CDs.

Using a simple MM approach interaction energy profiles of simple probes (C, CH_4, C_6H_6, H_2O, NH_4^+, and $HCOO^-$) passing through the center of the β-CD ring cavity along the main molecular symmetry axis were first evaluated by Chiellini *et al* [83]. Molecular Electrostatic Potential (MEP) values along the same path were also evaluated. The effect of the flexibility of the host β-CD molecule together with solute-solvent (H_2O) interactions have been presented by averaging structures of MD calculations for β-CD alone and β-CD surrounded by 133 H_2O molecules. The effect of various substitutions of β-CD has also been evaluated. Small symmetric hydrophobic probes (such as C, CH_4, C_6H_6) were predicted to form stable inclusion complexes with non-substituted and substituted β-CDs, the probe position typically being near the cavity center. The stability of the inclusion complexes will increase with increasing size and aliphatic character of the probe. Small polar and charged probes (such as H_2O, NH_4^+, $HCOO^-$) were predicted to prefer the interaction with the solvent (water) in the bulk phase rather than the formation of inclusion complexes with non-substituted and substituted β-CDs. Guest-host interactions in the stable inclusion complexes with hydrophobic probes are almost entirely dominated by dispersion interactions. The MEP reaches magnitudes close to zero in the center of the non-substituted β-CD ring cavity and in most of the studied substituted β-CDs and shows maximum positive or negative values outside of the cavity,

near the ring faces. Substitution of β-CD by neutral substituents leads to enhanced binding of hydrophobic probes and significant changes in the MEP profile along the β-CD symmetry axis.

MM simulations on the free non-substituted and substituted β-CDs were carried out with the Discover program (version 2.8.7) [82] using an all-atom model for the β-CDs and the probes. CVFF [84] and atomic charges, without non-bonding interaction cutoff were used consistently throughout this study. The crystal structure [85] of non-substituted β-CD was relaxed using an effective dielectric constant of 4 to account for the dielectric shielding. Initial optimization of hydrogen atoms positions was followed by steepest descendant and conjugate gradient minimizations of the whole β-CD molecule until convergence at the gradient of 0.04 kJ/(mol A) was reached. Substituted β-CDs were built from the minimized structure of non-substituted β-CD by adding molecular fragments of various structures of the O3 and O6 oxygen atoms in the selected α-D-glucopyranose residues of the β-CD ring using the Biopolymer module of the InsightII program [82]. The solvation Gibbs free energy of the considered probes was calculated in the framework of the Polarizable Continuum Model [86,87] with the dielectric constant of 80 representing water as the solvent and the model includes electrostatic, dispersion-repulsion and cavitation terms.

Authors derived the following main conclusions from the computer simulation of interaction energy profiles of simple probes passing through the center of the β-CD ring cavity:

- Small symmetric hydrocarbon (hydrophobic) probes (such as C, CH_4, C_6H_6) are predicted to form stable inclusion complexes with non-substituted and substituted β-CDs. Small polar and charged probes (such as H_2O, NH_4^+, $HCOO^-$) are predicted to prefer the interaction with the solvent (water) in the bulk phase rather than the formation of inclusion complexes with non-substituted and substituted β-CDs.
- Guest-host interactions in the stable inclusion complexes with hydrophobic probes are almost entirely dominated by dispersion interaction.
- Substitution of β-CD by neutral substitutents leads to enhanced binding of hydrophobic probes and significant changes in the MEP profile along the β-CD symmetry axis.
- Substitution of β-CD by substituents with charged side chains does not significantly affect the binding of hydrophobic probes (a slight increase similar to the non-charged substituents is observed), but has more important consequences for the binding of polar or charged probes due to large variations of the MEP inside and outside the ring cavity.

MM calculations with the Tripos Force Field [75] were employed by Pozuelo *et al* [88] to study the complexation of 4-(dimethylamino)benzonitrile (DMABN) and/or benzonitrile (BN) with β-CD. The studied systems have 1:1 (DMABN:β-CD and BN:β-CD, 2:2 (DMABN:β-CD) and 1:1:2 (DMABN:BN:β-CD) stoichiometries. Evidence for the formation of such complexes, binding constants and other thermodynamic parameters were extracted from the analysis of the steady state fluorescence measurements performed in a previous work [89]. The MM study, based on the energy changes upon

guest-host approaching, was performed *in vacuo* and in the presence of water as a solvent. Results showed that the driving force for 1:1 complexation is mainly dominated by non-bonded van der Waals host-guest interactions. However, the driving forces for association between 1:1 complexes to give 2:2 homo- or 1:1:2 heterodimers are dominated by non-bonded electrostatic interactions. Head-to-head electrostatic interactions between β-CDs, which are presumably due to the hydrogen bonding formation between secondary hydroxyl groups of CDs, are responsible for most of the stability of the dimers. The calculations were performed with Sybyl 6.3 program [90] using the Tripos Force Field [75]. The total potential energy of the system was obtained as the sum of six contributions: bond stretching, angle bending, torsion, van der Waals, electrostatic, and out-of-plane (for aromatic conjugated systems). Host (β-CD) and guest (DMABN, BN) geometries and charges were obtained from the AM1 method included in the MOPAC software [91]. Solvation was achieved by using the Molecular Silverware algorithm (MS) [92]. Periodic boundary conditions were employed using a cubic box with sides of 31.87 Å for any of the 1:1, 2:2 or 1:1:2 complexes studied. Numerical results showed that MM method is capable of predicting the experimental evidence [89]. Complexation or association does not seem to be accompanied by a noticeable increase in the strain or release of the CD macro-ring. As with other complexes, the water-complex interaction seems to render the uncomplexed form most stable. Relative binding energies for 1:1 complexes and dimers seem to explain the relative changes of enthalpy upon formation. Dimers have considerably more negative binding energies than 1:1 complexes. In the structures of minimum binding energies for dimers the DMABN or BN guests are sufficiently shielded from the solvent molecules to ensure that the strong loss in entropy during association should arise from the loss in the degrees of freedom of the associated dimer.

Azobenzene derivatives in solution present thermal *cis-trans* isomerization through the double bond –N=N– [93-94]. Sánchez and Rossi have studied the thermal *cis-trans* isomerization of azobenzene derivatives in a solution containing β-CD [95]. Experimental results showed that β-CD inhibited the isomerization process of some molecules whereas others were not affected, probably due to the presence of the organic cosolvent in the solution, which displaces the guest from the cavity and therefore promotes the formation of equatorial complexes. In order to analyze the main driving forces for the complexation and to gain some basic understanding of the experimental results, Castro *et al* performed a molecular modeling calculation of 1:1 and 1:2 β-CD/azobenzenes complexes [96, 97]. MM method was applied via the modified version of MM2 [77] contained in the commercial program "HyperChem® [98]. Theoretical results were in good agreement with experimental data found by Sánchez and Rossi [95] as well as with other accessible information on these complexes [99, 100].

Aicart *et al* analyzed the encapsulation of tolmetin, a nonsteroidal anti-inflammatory and anti-rheumatic drug, by β-CD from thermodynamic and structural points of view, by means of conductimetric and MM studies [101]. Conductivity measurements of aqueous solutions of tolmetinate (TOL^-) were performed as a function of β-CD concentration, at different temperatures ranging from 15 to 40 °C. The stoichiometry of the complex (1:1), its association constant K (~2000 M^{-1}), and the ionic molar conductivities at infinite dilution of the free ($\lambda°_{DRUG}$) and complexed ($\lambda°_{CD\text{-}DRUG}$)

drug were obtained from these conductivity data. A slightly negative change in enthalpy and a positive change in entropy, obtained from the dependence of K values with the temperature, revealed that both the enthalpy and the entropy favor the inclusion process. MM calculations also employed to study the complexation *in vacuo* and in the presence of water, showed that the drug prefers to penetrate into the β-CD cavity by the wider entrance, with toluol group entering first. From both MM calculations and experimental results, the hydrophobic effect and electrostatic interactions, possibly arising from the presence of intermolecular hydrogen bonds, seem to have a relevant role in the formation of the β-CD:TOL^- complex in aqueous media. Computational details are identical to those described previously by Pozuelo *et al* [88].

Noto *et al* have investigated the inclusion capacity of native β-CD and mono-(6-amino-6-deoxy)-β-CD versus aromatic compounds having a nitro or an amino group or both at three different pH values [102]. Molecular interactions in inclusion complexes have been also studied by means of MM (MM2/QD) models. Electrostatic and van der Waals interactions and the formation of the hydrogen bond between the donor amino group and the oxygen atom of the secondary hydroxyl group seem to be the more important contributions in determining complex stability. This study was based on the need to know the relative changes taking place in the inclusion process when one modifies one or more functional groups in the host molecule. In fact, from a thermodynamic point of view it has been proposed to dissect the inclusion process in a series of ideal steps which can be summarized as: a) desolvation of the guest; b) internal desolvation (partial or total) of the host cavity; c) inclusion of the guest; d) reorganization of the solvent pool [103]. This scheme provides the general basis to discuss the role of a given effect in the process. At present, only a limited number of systematic thermodynamic studies using modified CDs have been reported [104-109]. Noto *et al* selected six aniline derivatives, and for comparison nitrobenzene, *p*-nitroethylbenzene, and *p*-nitroisopropylbenzene as guest molecules. The guest molecules were chosen so as to have variations in molecular properties such as, for example, dipole moment, molecular volume, ability to act as hydrogen bond donor/ acceptor, and solvation capability. Binding constants were measured from absorption spectra at 298 K in phosphate buffer aqueous solution at pH 6, 8, and 11. Data reported in Noto's work have shown that the inclusion process depends strongly on the host structure; in this case substitution of a primary hydroxyl group for an amino group decreases the ability of the host to include a guest. Finally, it seemed that for the substrates examined there is no obvious hierarchy among the factors (except for the not very important steric strain) that govern inclusion process.

Since the size and shape of the cavity of CDs play an essential role in the formation of these inclusion complexes, there is strong interest in modifying the size and shape of such cavity, either by single or multiple substitution [110], capping [111], and changing the configuration [112], or by combining structural elements of CDs with noncarbohydrate moieties, as in the glycophanes [113], glyco-crown ethers [114], and cyclic acetyleno- saccharides [115-117]. Recently, Vasella *et al* reported the synthesis of CD analogues containing a buta-1,3-diyne-1,4-diyl or a butane-1,4-diyl unit [118]. MM3 force-field calculations were made and they demonstrated the strong influence of the configuration and constitution of the γ-CD analogues on the shape of the cavity. Gas-

phase possible ring conformations of several γ-CD analogues were obtained by molecular modeling via Macromodel V. 7.0 with a modified MM3 force field [63]. The minimal-energy conformations of these analogues lack any strong ring strain but indicate significantly different shapes.

Hydrolysis of *p*-F, *p*-Cl, and *m*-Cl phenyl trifluoroacetates was studied in the presence of β-CD. The reactions are inhibited by β-CD at pH 6 while they are catalyzed in alkaline solution [119]. MM3 calculations reproduced some of the experimental results. The substrates form inclusion complexes with β-CD, which are of similar stability as those of the corresponding acetates. However, the association of the transition state is less favorable in these reactions than in those of the acetates, and consequently less strong catalysis is observed. The inclusion of phenyl acetate and phenyl trifluoroacetate into the β-CD cavity was emulated following previously described methodology [38,120] using Allinger´s MM3 force field [64]. Results indicated that the less efficient catalysis by β-CD for the reactions of trifluoroacetate esters compared with acetate esters is not due to different modes of inclusion of the substrates as previously suggested [121] but to smaller stabilization of the transition state for the perfluorinated esters. This effect can be attributed to steric factors because the CF_3 group has a considerable higher van der Waals volume than the CH_3 [122], and so the transition state for the reaction with β-CD is more sterically hindered than that of the corresponding acetate.

Saenger *et al* have carried out MD and Monte Carlo (MC) simulations of β-CD and its per-dimethylated derivative hepta-kis(2,6-di-*O*-methyl)-β-CD (DIMEB) in water solutions at two temperatures, 25°C and 70°C [123]. The structure of the hydration shells, as well as the solute solvent and solvent-solvent correlations have been analyzed. The negative solubility coefficient of DIMEB is conditioned first of all by progressive destruction of the hydration shells around its methyl groups with temperature increase, whereas for β-CD with positive temperature coefficient, solution is comparable at 25°C and 70°C. To choose a suitable force field when carrying out a molecular modeling study of carbohydrates is not trivial [124], and there are still ongoing studies trying to systematically improve existing force fields [125,126]. One of the most important weaknesses of the vast majority of the existing carbohydrate force fields is their inability to correctly describe both conformational preferences of carbohydrates and their intermolecular interactions (*e.g.* hydration preferences) simultaneously [124]. With this in mind, Saenger *et al* employed the OPLS-AA force field by Jorgensen *et al* [127], since due to its design it is equally useful in describing both intra- and intermolecular interactions for a very wide range of organic molecules. Both in MC and in MD simulations, DIMEB and β-CD were considered fully flexible (no constraints for bond lengths, bond and/or torsion angles). MC simulations have been carried out using the MCPRO16 routine by Jorgensen [128], while MD simulations were performed using the CHARMM26 routine package [129]. Authors noted a qualitative correspondence between the MC and MD results that increases the reliability of their conclusions. The data presented can explain the negative solubility coefficient of DIMEB and the preponderance of the hydrophobic effect at elevated temperatures. They have also found that the number of water molecules in the integral hydration shell around DIMEB drastically increases with temperature. This is another characteristic feature of the

hydrophobic effect at the molecular level [130], namely the increase in water ordering which results in larger clusters and larger density fluctuations at the microscopic scale and thus in an increase of the probability to form appropriately sized cavities to accommodate the solute molecules. Thus, in actual aqueous solutions of DIMEB, the temperature increase leads to the formation of cavities suitable to host DIMEB molecules, underlining their hydrophobic nature. It is clear that the mobility of the cavities containing DIMEB molecules should also increase with temperature, and the probability of collisions among dehydrated DIMEB molecules (*i.e.* the probability of their aggregation) increases as well. According to their simulation results, this is apparently not the case for β-CD, which becomes even better integrated into the water H-bonded framework with increasing temperature.

An interesting alternative method to study molecular interactions of CDs inclusion complexes was recently published by Cai *et al* [131]. In fact, molecular interactions of inclusion complexes of mono- or 1,4-disubstituted benzenes and α-CD have been studied by means of two types of energy terms in the total interaction energies, a non-bonded term and a desolvation term, and minimized by a genetic algorithm (GA). Using the consistent force field (CFF91), the non-bonded energies between all pairs of atoms in different molecules were determined by a Coulomb potential term for electrostatic interactions and a Lennard-Jones potential for van der Waals interactions. The desolvation energy term was modeled by a simple constant term corresponding to a penalty when polar atoms are placed in the hydrophobic cavity. The total interaction energies for 15 inclusion complexes with experimental association constants (ln K) were optimized by the GA method. Linear regression analysis of the observed association constants against the total energies was performed. It was found that the interaction energies of these complexes obtained by the simple interaction energy model can be correlated with their experimental association constants, and also the desolvation term should be included.

A GA was introduced by Holland in 1975 [132] as a probabilistic search technique. It starts from an initial population, evolves by exploitation and exploration acting on chromosomes, and finally finds the best solution to a problem. The exploitation procedures select parents from the population according to their fitness values. The exploration procedures including recombination and mutation are operated on the parents´ chromosomes to generate a new population with a certain probability. Due to the advantages of global and parallel searching ability, GA has been applied to many complicated optimization tasks, such as geometry optimizations for structures [133,134].

The energy model described by Cai *et al* [131] is reliable and a combination with the GA program is convenient to predict the inclusion stability for complex between mono- or 1,4-disubstituted benzenes and α-CD. It may provide an alternate tool to study the interactions of the host-guest systems. The calculation results give a good relationship between observed ln K values *vs* the total energies minimized. The linear regression results also suggest the van der Waals interactions are more important than the electrostatic interactions, which is in agreement with their previous studies [135]. The desolvation effects determine the orientation of the guest molecule with polar atoms in the hydrophobic cavity of α-CD.

The formation of 2:1 and 2:2 CD-complexes requires the association of two CD units. The formation of aggregates in aqueous solution of pure CDs has been experimentally detected [136,137], but the driving force for this aggregation has never been systematically studied. Jaime *et al* addressed this problem studying the α-, β-, and γ-CD dimers by MM and MD calculations, the relative stability of dimers and the involved molecular interactions having been determined [138]. Three possible orientations were considered for the dimers: the head-to-head, the head-to-tail, and the tail-to-tail. *In vacuo* MM calculations were used to obtain the most stable arrangements, and MD simulations were performed over all energy minima obtained for each dimer. Results from MD always showed head-to-head orientation as the most stable as a result of the larger number of intermolecular hydrogen bonds present. The conformation of the dimers was minimized using the original MM3(92) [139] force field [64]. MD simulation runs were performed over each of the energy minima obtained by the preceding method and AMBER* force field [140,141] as included in the Macromodel V.5 package [63], was used for the MD simulations. The binding energy was computed to be around 126-209 kJ/mol, depending on the CD and orientation. The structure of β-CD does not change much on dimerization. Interestingly, γ-CD dimers contain two diametrically opposed glucose units not aligned with the rest of the glucose units, in agreement with the experimental results found for ε- and ι-CD. This finding suggests that this phenomenon is general among CD systems.

Computational studies for interpreting spectral data

A considerable research effort has been made in recent years to enlarge the field of the utilization of CD, mainly by means of selective modifications of their structure. One area, which appears particularly promising, is that of supramolecular photochemistry [142], since these macro-cycles can be functionalized with photoactive units affording supramolecular photoreceptors possessing unique properties. β-CD is, probably, for cost and dimension of the cavity, the best choice from the point of view of the macro-cycle and, in fact, most of the attempts made to date were based on the use of this CD. Marcuzzi *et al* have reported the synthesis and computational study of a capped multifunctional supramolecular receptor: heptakis-(6^A,6^C-4,4′-dicarboxyamido-2,2′-dipyridyl)-6^A,6^C-deoxy-6^B,6^D,6^E,6^G-pentamino-β-CD). This compound was characterized by spectroscopic methods and by semiempirical calculations carried out using the AM1 method [143]. The aim of this work has been to design a suitable receptor, which could combine the capability of the CD to include guest molecules with the known ability of 2,2′-dipyridine molecules to promote complexation of metals and photochemical reactions. Experimental and theoretical methods suggested an A, C substitution in the capped β-CD. The spectroscopic data of the new molecule were substantially in good accord with a 1:1 capped derivative and the main problem was to assign the structure since, in principle, three different regioisomers are possible, depending on where the trans-annular linkage is formed. This issue was analyzed via NMR, which rendered a satisfactory answer (*i.e.* en A, C substitution in the capped β-CD). The AM1 semiempirical calculations have shown that the A, C capped β-CD is significantly lower in energy than the A, B and A, D isomers. This preference is about 20 kcal/mol regarding the enthalpy of formation. MO calculations were performed using Spartan 3.1 software

[144]. The ability of the new compound to coordinate metal ions was tested in preliminary experiments with Cu^{2+} and Zn^{2+}. In both cases, bathochromic shifts to the typical dipyridine adsorption bands at *ca.* 216 and 300 nm were observed in aqueous acidic solution.

Waldeck *et al* [145] have combined static and time-resolved spectroscopic techniques to obtain information about the structural and dynamical features of the intermolecular complex in order to explore in a rather satisfactory way the dynamical behavior of these complexes. This study explores the effect of the charge and the size of the guest molecule on the behavior of the complex. The influence of the charge is investigated by comparing the properties of the complex formed between resofurin (an anion) and β-CD to that formed between oxazine-118 (cation) and β-CD. The resofurin anion and oxazine-118 cation have similar size and shape. The influence of size was studied by comparing the structural and dynamical properties of the complex formed between β-CD and oxazine-118 with that formed between β-CD and the larger in size oxazine-725. The time-resolved optical heterodyned polarization spectroscopy technique (OHPS) [146-149] was used to measure the rotational relaxation time of the chromophore in water and in the presence of the CD. Besides, usual measurements of UV-VIS and NMR spectra were recorded for the free guest and host in water as well as for the solutions with host-guest ratios 1:1 and 100:1. Molecular modeling studies were performed in vacuum with empirical force fields [150] and semiempirical quantum theory using the AM1 hamiltonian [81]. The initial docked structure of the inclusion complex of resofurin and β-CD was obtained using the simulated annealing method, with a rigid geometry and fixed partial charges for the individual molecules. The calculations were performed using HyperChem® [151], Mopac93 [152] and an in-house program for simulated annealing [150]. This study demonstrated that the host-guest complex is bound for time scales in excess of a few nanoseconds but shorter than a few microseconds. It was also shown that the electrostatic properties of the guest do not affect the internal rotational motion of the guest in the complex, but the relative host-guest size determined the character of intermolecular host-guest dynamics.

Marsura *et al* [153] have achieved successfully the synthesis of six new "bridged" β-CD dimers by two-to-one reactions from β-CD and 6^{A}-azido-6^{A}-deoxy-β-CD. NMR data, along with MM calculations, suggested a ´helical-like´ arrangement for the phenanthroline-diyl-linked "dimer" derivative. Complexation properties of this molecule were established by UV-VIS-spectrophotometric titration toward four metals. In addition a specific and interesting esterase activity toward the phosphodiester bond of bis(4-nitrophenyl) phosphate anion was found in the case of the C^{II} complex. The relative complexity of the synthesized molecules made interpretation of their ^{1}H-NMR spectra speculative. Therefore, 2D-NMR methods were essential for resonance attributions. Moreover, to obtain fundamental information on the molecular conformation in solution, several techniques were used: COSY-DQF (double quantum filtration correlation spectroscopy), NOESY (nuclear *Overhauser* spectroscopy), ROESY (rotating-frame *Overhauser* spectroscopy), and TOCSY (total-correlation spectroscopy). MM3 calculations were effected for some complexes and supplementary MD computations were conducted using software from Biosym/MSI of San Diego-Dynamics. Calculations

and minimization were done with the Discover® program [154] using the CVFF force field.

Takeshita *et al* [155] have studied the effect of inclusion of diarylethenes in CDs cavities on cyclization quantum yields and on circular dichroism spectral changes by photoirradiation. The addition of β- and γ-CDs to an aqueous solution of the open-ring form of 2,2′-dimethyl-3,3′-(perfluorocyclopentene-1,2-diyl)bis(benzo[b]tiophene)-6-sulfonate) **(1)** increased the ratio of the antiparallel conformation. The enrichment of antiparallel conformation caused an increase in the photocyclization yield of **(1)**. The circular dichroism spectral intensity of **(1)** or 2,2′,4,4′-tetramethyl-3,3′-(perfluorocyclopentene- 1,2-diyl)bis(tiophen-5-yl-(phenyl-4-sulfonate)) **(2)** and CDs in aqueous solution increased with the increasing concentration of CDs. The induced circular dichroism spectrum of **(1)** in β-CD reversibly changed from negative to positive by UV irradiation. The spectral change was attributed to the change in the direction of transition moment of **(1)** in the cavity. To clarify these circular dichroism spectral changes by irradiation, the transition moments of the open- and closed-ring forms of a diarylethene were calculated as a model for simplifying the calculations, which were carried out by the AM1-RPA method [156]. These calculations of the transition moments confirmed that the photoreversible circular dichroism spectral change is due to the change in the direction of the transition moments of diarylethene by photoirradiation.

The polymerization behavior of hydrophilic CD complexes of methacrylamide monomers, which are N-substituted with long alkyl- or carboxyalkyl chains was reported by Ritter *et al* [157]. The influence of the hydrophilic CD as host on the reactivity of the more hydrophobic monomers as polymerizable guest components was investigated using water as solvent. The authors incorporated the hydrophobic monomers N-methacryloyl-11-aminoundecanoic acid **(3)** or N-methacryloyl-1-aminononane **(4)** as guests into the cavity of heptakis(2,6-di-*O*-methyl)-β-CD (Me_2-β-CD) as a host, yielding the water compatible monomers **(3)**/Me_2-β-CD complex **(5)** and (4)/Me_2-β-CD complex **(6)**. These complexes were polymerized radically in aqueous medium. The resulting polymers **(7)** and **(8)** which were obtained from the complexes **(5)** and **(6)**, are insoluble in water because of the unthreading of the CD during the polymerization. The polymerization rate of **(5)** and **(6)** is high in comparison to the rate of the uncomplexed monomers **(3)** and **(4)** in solution. In addition, also the yields and viscosities of the polymers **(7)** and **(8)** prepared from complexes monomers in water are significantly higher than the corresponding values of polymers prepared in solution. To determine the most preferred location of the CDs in the complex, ^{1}H NMR spectroscopy was applied. A computer-generated structural model of complex **(5)** allowed the authors to verify that the probability of homopolymerization of the complexes may be low due to the huge and room filling CD. In contrast to this prediction it was found that the complexes **(5)** and **(6)** could be homopolymerized very well, either in water or in water/dimethyl sulfoxide solution (1/4 v/v) initiated with the free radical redox initiator $K_2S_2O_8$/$KHSO_3$ in all cases. Modeling was performed on the MM+ level through the HyperChem® package [151].

Optimal and safe use of vitamin D_3 (VD_3) in pharmaceutical and food industries requires imperatively solving the problem of its stability and its dispersion within complex matrices such as drugs and foodstuffs. Inclusion complex formation with CDs

seems to be the best solution. At industrial scale, the final product is a solid form. Siouffi *et al* [158] investigated UV/VIS spectrophotometry, IR spectroscopy, ^{1}H and ^{13}C NMR, mass spectrometry and X-ray diffraction in order to determine the most appropriate technique for the characterization of the solid inclusion complex of VD_3 by either β-CD or γ-CD. They used molecular modeling under GENMOL® to continue to explore the inclusion of VD_3 and its most important metabolite in these CDs. The molecular modeling allowed the authors to apprehend VD_3 ordering inside CDs. Theoretical calculations showed that trimolecular assemblies are very favorable: association energy for VD_3/γ-CD inclusion compound was estimated at –36.3 kcal/mol. VD_3/β-CD inclusion compound seems to be slightly more stable with an association energy estimated at –37.5 kcal/mol because of the smaller size of the β-CD cavity than that of the γ-CD. It seems that this ordering does not allow water molecules entering the complexes. Stability of the suggested trimolecular assemblies depends on inter- and intramolecular hydrogen bonds between VD_3 hydroxyl (C3) and one of CD primary hydroxyls, between both CD hydroxyls and between hydroxyls of each CD. Molecular modeling allowed also the authors to apprehend the molecular assembling between CDs and calcidiol, one of the most important VD_3 metabolite.

Aki *et al* [159] have investigated by microcalorimetry, ^{13}C-NMR spectroscopy and MD simulations the inclusion complexes of phenobarbital (PHB) with 2-hydroxypropyl-β-CD (HPCyD) in aqueous solution. Two different types of PHB-HPCyD inclusion complexes at 1:1 stoichiometry were realized by un-ionized PHB. In the first type of inclusion with higher affinity with HPCyD, the phenyl ring of PHB was included within the HPCyD cavity, whereas in the second type, the barbituric acid ring seemed to penetrate into the cavity. The ethyl side-chain remained outside the cavity in both types. Complexation was independent of the concentrations of both PHB and HPCyD. ^{13}C-NMR chemical shifts of barbituric acid ring and of a phenyl ring substituted at C5 on barbituric acid ring were significantly moved up-field upon penetrating into HPCyD cavity. MD simulations of PHB-β-CD inclusion complexes in aqueous solution were performed using the AMBER program (version 4.0) [160,161]. The geometries of β-CD and PHB were optimized using the MM3 program [64]. MD simulations were done via MC technique and they suggested that the PHB-β-CD inclusion complexes are stable in aqueous solution, at least through the 30 ps simulation time. In the chemical structure of HPCyD, 2-hydroxypropyl groups are linked to the primary side-chains of β-CD. The phenyl ring of PHB easily penetrated into the cavity from the secondary hydroxyl side of HPCyD. These results agree with experimental data.

Kodaka derived a general rule for the inversion of circular dichroism (ICD), which is based on the coupled-oscillatory theory [162]. Later on, he applied it to explain the ICD observed in the complexation of s-substituted naphthalene (2-naphtol, 2-methyl-naphthalene, 2, chloronaphthalene, 6-bromo-2-naphthol) with α- and β-CDs, where the substrates are included deeply in the cavity of β-CD but only partly included in the cavity of α-CD [163]. The absorption wavelengths and directions and oscillator strength of the transition moments of the naphthalene derivatives were obtained by INDO/1 calculation in ZINDO (version 3.6) of the CAChe system (SONY Tektronik). In the configuration interaction calculation, 82 configurations were considered. The structures were optimized by AM1 before INDO/1 calculation. The molecular modeling consideration suggests that

the substituted naphthalene can be included axially and completely in β-CD but only partially in α-CD. Besides, the calculated wavelengths are well compatible with the observed ones. These successful results in the interpretation of the ICD inversion phenomena proves the validity and usefulness of the general rule cited above [162].

Lucarini *et al* [164] have used EPR spectroscopy to study the inclusion of the nitroxides $PhCH_2N(O^{\cdot})tBu$ **(9)**, $CH_3N(O^{\cdot})tBu$ **(10)** and $PhCH_2N(O^{\cdot})CH_3$ **(11)** by α-CD, β-CD, γ-CD, and by chemically modified β-CDs in aqueous and aqueous-methanolic solutions at 294-356 K. The nitrogen and β-proton hyperfine splitting for free and included nitroxides differed significantly especially for **(9)**. Equilibrium measurements of the concentrations of free and included radicals afforded binding constants for the nitroxides. Selective line broadening was also evident in the EPR spectra, and this was attributed to modulation of the spectroscopic parameters by exchange between free and included nitroxides. Computer simulation of these spectra enabled the rate constants for association and dissociation to be determined. These nitroxides are particularly suitable probes for the study of inclusion by CDs and probably by other complexing agents, because free and complexed nitroxides have spectroscopic parameters that differ significantly more than those of all other radicals used previously for this purpose. The rate constants for association and dissociation were determined as a function of temperature by simulating the exchange-broadened EPR spectra with well-established procedures [165] based on the density matrix theory [166,167] and by assuming a two-jump model. Fitting to the experimental spectra was carried out with a MC minimization procedure [168]. The authors obtained an excellent agreement between simulated and experimental spectra recorded at different temperatures in the presence of 3.25×10^{-3}M β-CD and they concluded this method for investigating the dynamics of CD host-guest interactions has considerable potential.

In the common α-, β-, and γ-CDs glucose units are "locked up" in a straitjacket type belt [2-6] so that their macro-cycles exhibit remarkable structural rigidity. However, if low-molecular-weight CDs are to be *realistic* enzyme models, flexibility has to be introduced into their macro-cycles so that they can mimic the dynamic induced-fit mode of action rather than the stationary lock-and-key approach. With these considerations in mind, Fujita *et al* have undertaken studies of the inclusion complexation properties of CDs in which one [169,170], two [171], or with all glucose units [172-174] converted into altropyranose residues, which have been shown by calculation [175,176] and by NMR [177] evidence to have flexible conformation. As a result of these studies, they have reported on the inclusion of adamantine-1-carboxylate into mono-*altro*-β-CD **(12)**, representing thus the first example of a guest-induced fit into a cyclooligosaccharide host. For an assessment of the overall molecular shape of **(12)**, its cavity dimensions, and its potential for the formation of inclusion compounds, the molecular contact surface was generated as well as its molecular lipophilicity profile, based on MD simulations in water. ^{1}H NMR spectroscopy was applied to make experimental determinations. Calculations of the molecular contact surfaces and the respective hydrophobicity potential profiles were performed using the MOLCAD [178,179] molecular modeling program and its texture mapping option [180]. Scaling of the potential profiles was performed in relative terms (most hydrophilic to most hydrophobic surface regions).

CD inclusion complexes with water and ethanol, both of which have been known to form cage-type crystal structure in the three-dimensional crystal growth mode, were observed to form new self-assembled structures on highly oriented pyrolite graphite (HOPG) and MoS_2 surfaces [181]. By removing the surface CD molecular layers using the atom manipulation technique of scanning tunneling microscopy (STM), ordered stacking of the inner layers was observed. The anisotropic hydrogen bonding interaction between CDs induced the surface of the observed CD layers, which is possibly related to the two-dimensional crystal growth mode. On MoS_2, CD has threefold symmetry lattice matching commensurate with the structure of S atoms, which is considered to affect the ordering of the self-assemblies. In fact, numerous defects were observed in the surface layer. From the analysis based on the observed STM images, ordering of the self-assembled structures on HOPG and MoS_2 surfaces was concluded to take place in the two-dimensional growth mode. Some preliminary theoretical studies of Yasuda *et al* [181] on the electronic structures of self-assembled CDs allowed them to calculate frontier highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for α-CD with the same conformation as the α-CD-H_2O complex. They derived the conclusion that electronic structure is rather metallic, and bias dependence of the STM image is unclear. The obtained results suggested that CDs in the assembled structures have an electronic structure different from that expected form a single molecule.

A novel fluorescent probe with n,π* configuration, the azoalkane 2,3-diazabicyclo [2.2.2]oct-2-ene (DBO), is responsive to complexation by supramolecular hosts. The n,π* fluorescent probe serves to provide structural and, owing to its exceedingly long fluorescent lifetime (up to 1 μs), also kinetic information on host-guest complexation. The three CDs were selected as prototypical hosts in aqueous solution, and the complexation, in both the ground and excited states, was followed by four techniques: time-resolved and steady-state fluorescence, UV absorption spectroscopy, and NMR spectroscopy [182]. The fluorescence quenching rate constants of DBO by α-, β-, and γ-CD were determined from the dynamic component of the bi-exponential time-resolved decay traces, while the static component was assigned to the fluorescence lifetimes of the complexes of α-CD and β-CD. Time-resolved and steady state fluorescence measurements yielded consistent results. The shorter lifetimes in the complexes are attributed to the propensity of singlet-excited DBO to undergo fluorescence quenching by an “aborted” hydrogen abstraction with the labile glycosidic C-H bonds inside the cavity. Ground-state binding constants could be determined by both UV spectroscopy and, owing to the high water solubility, also by NMR spectroscopy. The spectroscopic data support the formation of *inclusion* complexes in both the excited and ground states. The dynamic quenching was attributed to inclusion with subsequent quenching inside the shorter-lived complex. The examination of the complexation dynamics at high guest (DBO) concentration revealed an unprecedented behavior, which may be indicative of singlet energy transfer between the free DBO and the CD-DBO complex. The formation of a 1:1 inclusion complex in the ground state was supported by the results from molecular modeling using the AMBER-S force field [183] included in the HyperChem® software [184]. Since bicyclic molecules are not well parametrized in AMBER-S, the DBO geometry was kept frozen in the AM1 optimized geometry, which closely

resembled the experimental gas-phase structure. The geometries and dipole moments of the DBO ground and triplet states were also calculated at (U)B3LYP/6-31G* levels of density functional theory by using the Gaussian 94 package [185]. This formation of an inclusion complex is in agreement with the NMR data. The DBO molecule preferred a relative conformation with both azo nitrogen atoms directed toward the tighter cavity opening.

The proton chemical shifts of propantheline bromide (PB) and α-CD were determined as a function of the PB concentration in the absence and presence of 5 mmol/dm^3 α-CD [186]. The chemical shift variations of PB protons induced with the dimerization of PB agreed very well with the values calculated on the basis of the antiparallel stacking of two xanthene rings. The 1:1 binding constant and the chemical shifts of PB and α-CD protons for their complex were evaluated from the concentration dependence of the chemical shifts. On the basis of both these shift data and MM calculations, it is estimated that one of the benzene rings of PB in the complex is included shallowly from the wider side into the α-CD cavity. Chemical shifts of the α-CD protons, calculated for this structure on the basis of the current effect of the xanthenes, agreed quite well with the observed ones. MM Calculations of the complex were performed with the Biosym Insight II/Discover (95.0) [154]. The Discover CVFF force field was used for energy minimization. All calculations were made in the presence of water. The partial atomic charges and the structure of PB *in vacuo* were obtained by optimization using AMPAC/MOPAC module of Insight II with PM3 and potential types were derived from the CVFF force field. The optimized structure of PB was then soaked in a 1 nm layer of water an then its total conformation energy was minimized. The starting structure of α-CD molecule was the published coordinates of the X-ray structure of α-CD.6H_2O [85]. This structure was then soaked in a 2 nm layer of water and minimized the total conformational energy. This minimization produced little changes in the structure.

Mendicuti *et al* used steady state fluorescence and MM calculations to study the inclusion complexes of 9-methyl anthracenoate (MA) and 1-methyl pyrenoate (MP) with β-CD [187]. Binding constants of 1:1 complexes at different temperatures were obtained from the analysis of the fluorescence enhancement of the β-CD solutions with respect to the MA or MP free chromophores. The thermodynamic parameters ΔH and ΔS were also obtained and they predicted both complexes to be thermodynamically stable. Analysis of the thermodynamic factors governing the stability demonstrated that entropy is more important than enthalpy in determining the stability of these complexes. MM calculations were applied to study both inclusion processes *in vacuo* and in the presence of water as a solvent. Complexation was determined to be due to non-bonded van der Waals host-β-CD interactions. Both MA and MP penetrate only partially into the β-CD cavity. The calculations *in vacuo* and in water as a solvent were performed with Sybyl 6.3 [90] and the Tripos force field [75]. Geometry and charges of β-CD, MA, MP, and water molecules were obtained by MOPAC [91]. The structure of the complexes agreed with the sign of the entropy upon complexation and with the suggestion that the ability of the CD cavity to insulate the guest from the solvent is the main consequence of the sign and value of ΔS.

The inclusion complex of salbutamol and β-CD was studied by computational MM2 and PM3 methods and experimental techniques [188]. Molecular modeling calculations predicted two different orientations of salbutamol in the β-CD cavity *in vacuo* an in aqueous solution. *In vacuo* calculations showed that the introduction of the aromatic ring of salbutanol is preferred to the introduction of the *tert*–butyl group into the β-CD cavity. However, in aqueous solution both computational methods predicted the introduction of the alkyl chain instead of the aromatic ring in the β-CD cavity contrary to experimental results published previously. These quantitative predictions were experimentally confirmed by studying the inclusion complex in solution by NMR. A 1:1 stoichiometry was found by ^{1}H NMR studies for this complex. A 2D ROESY experiment showed that there are no cross-peaks between the aromatic protons of salbutamol and any of the protons of β-CD. Cross-peaks for the protons of the *tert*-butyl group and protons inside the cavity of β-CD demonstrated the full involvement of this group in the complexation process and confirmed the orientation of the complex predicted by molecular modeling. The solid-state complex was prepared and its stoichiometry (β-CD.$C_{13}N_{21}NO_3$.8H_2O) and dissociation process studied by thermogravimetric analysis. The most important conclusion of the current work was addressed to the use of molecular modeling techniques in predicting the orientation geometry of β-CD inclusion complexes. Taking into account that most of these complexes are studied by NMR techniques in solution, the importance of explicitly or implicitly considering the solvent in these calculations is obvious. Finally, authors pointed out that at present, several treatments of solvent in computational techniques are available at different levels of theory, and the use of them studying β-CD inclusion complexes in solution is strongly recommended.

The first volume profiles for complex formation of α-CD with 4 diphenyl azo dyes (S) were presented as a new approach to understanding inclusion phenomena [189]. The behavior of the dyes alone was first studied in aqueous solutions to rule out any competition reaction. Under the experiment conditions used for the stopped-flow kinetics studies, it has been proved than only monomeric species were present (no aggregation of the dye was formed by π-π stacking interactions). NMR experiments and kinetic evidences have shown that only directional binding of the dye via the sulfonate/sulfonamide group through the wide rim of the α-CD was possible. The 1:1 complex was the only stoichiometric species formed. The inclusion reactions for the four selected dyes were characterized by a two-step kinetics described by a first fast step that yields the intermediate S.α-CD*, followed by a slower rearrangement to form the final complex, S.α-CD. 2D NMR experiments served for a MD calculation leading to a structural representation of the intermediate and final complexes. An interpretation of the volume profiles obtained from high-pressure stopped-flow kinetic experiments have not only confirmed the so far proposed mechanisms based on “classical” kinetic investigations but offered a new focus on the inclusion process. The inclusion mechanism can be summarized now as follows: the complexation begins with an encounter of the dye and α-CD mainly due to hydrophobic interactions followed by a partial desolvation on the entering head of the dye. The latter interacts with the two “activate” inner water molecules of the free host and the primary hydroxyl group barrier of the α-CD delays

their complete release. At this first transition state, a squeezed arrangement develops inside the cavity inducing a negative activation volume. The subsequent intermediate is characterized by a total release of the two inner water molecules and interactions of the dye head with the primary hydroxyl groups of the host in a trapped-like structure. The latter interactions and concurrent tail interaction with the secondary hydroxyl groups of the host lead at different extents to a strained conformation of the host in the second transition state. In the final complex, the head of the dye is totally re-hydrated as it protrudes from the primary end of the host cavity, which can now adopt a released conformation.

Simulations were done using the program CVFF [190] force field as implemented in Discover (version 97; Molecular Simulations, 1997), starting from structures of α-CD and one dye, including the corrected NOE constraints obtained from the ROESY spectrum. The MD runs were run using standard Discover protocols at a constant temperature of 300 K.

Dodziuk *et al* [191] have investigated the dynamic stereochemistry of amphiphilic derivatives of α-, β-, and γ-CD by means of variable temperature ^{1}H and ^{13}C NMR spectroscopy in DMF-d_7 solutions. The most significant spectral changes were detected for the smallest hexakis(6-deoxy)-α-CD and they decrease with the increase of the macro-cycle size. On the basis of ROESY measurements, these changes reflecting restricted movements of tiophenyl groups upon the temperature decrease were interpreted in terms of self-inclusion of at least one tiophenyl group. Molecular modeling of these compounds was consistent with these findings. MM calculations were carried out with the aid of MMX force field incorporated into PCMODEL program [192].

Ueno *et al* have indicated that many appending moieties of modified CDs tend to be included in the CD cavity, forming self-inclusion complexes [193-195]. Since the stability of the self-inclusion complexes have not been discussed until recently, Ueno *et al* have analyzed in detail to modified CDs bearing the *p*-dimethylaminobenzene moiety as the primary hydrocyl side. One of the modified CDs was 6-deoxy-(6-*p*-dimethylaminobenzoyl) -amino-β-CD (DMAB-β-CD) and the other was 6-deoxy-(6-*p*-dimethylaminobenzene butyryl)-amino-β-CD (DMBP-β-CD). The conformation of DMAB-β-CD had been analyzed previously [196] and it had been found that it takes a self-inclusion form in aqueous solution although there exists an equilibrium between two forms with the appending moiety inside (form A) and outside (form B) the CD cavity. Furthermore it was estimated by CPK model analysis that the formation of the self-inclusion complex is rather difficult for DMAB-β-CD because of the limited ability of the DMAB moiety to be included in DMAB-β-CD. On this basis, Ueno *et al* have considered interesting to examine the stability of self-inclusion complexes on the modified CDs with and without a flexible appending moiety [197]. The stability of the self-inclusion complexes was measured by fluorescence decay analysis, via absorbance, fluorescence, circular dichroism, ^{1}H NMR and time of flight mass spectra. Analysis by MD and MM calculations on the formation of self-inclusion complexes were performed in this study. These results provided interesting information on the conformation of modified CDs. The energy surfaces of DMAB-β-CD and DMBP-β-CD were explored in a random way using a MD conformational search [198]. The calculations in this study were carried out under pseudo vacuum conditions, using the distance-dependent-

dielectric condition to compensate for the lack of explicit water. The analysis of theoretical results clearly indicated that the total energy of form A is lower than the B form for both complexes, so it was concluded that form A would be more stable species for the two compounds. These calculated results were in good agreement with the experimental results. All these analysis demonstrated that the stability of the self-inclusion form depends on the appending moiety, specially the flexibility of the moiety.

Stoddart *et al* [199] have described the preparation, isolation, and characterization of two novel β-CD derivatives, per-substituted with mono- and disaccharide residues, respectively, by means of short spacer arms. Their synthetic methodology is a useful addition to the growing literature of carbohydrate cluster compounds in that it is a simple and potentially flexible method for the attachment of carbohydrate residues to the primary faces of CDs. The association constants for the complexation of the anti-inflammatory drug naproxen in β-CD, per-2,3-dimethyl-β-CD and β-CD per-substituted with seven thio-β-D-lactosyl units in 0.01 M phosphate buffered saline solution (pH 7.4) were determined by the UV-VIS spectrophotometric titration, and results indicated that compounds such as the lactose cluster of β-CD possess the ability to complex drug molecules. By tailoring the appended carbohydrates to match specific cell-surface carbohydrate receptors, it is hoped that compounds of this type will be able to deliver drug molecules to cells in a highly selective manner. In order to gain some insight into the three-dimensional structure of β-CD derivatives per-substituted via seven thio-β-D-glucosyl **(13)** and lactosyl units **(14)** in aqueous solution, a computational study was performed utilizing MD, as implemented in the program Macromodel 5.0 [63], which provides a "snapshot" of their structures. The investigation revealed that **(13)** is approximately 23 Å in diameter and approximately 19 A in height. Likewise, **(14)** was found to be slightly larger, 27 Å in diameter and again approximately 19 Å in height. In both cases, the CD torus was found to possess a distorted elliptical shape, which is not surprising on account of the absence on inter-glycosidic hydrogen bond of the CD tori, as a result of all secondary face hydroxyl groups having been methylated.

Raman spectra of benzaldehyde (B), 4-methoxybenzaldehyde (4MeOB), 3-methoxybenzaldehyde (3MeOB), 3-methylbenzaldehyde (3MB) and 3-chlorobenzaldehyde (3CB) included in α-CD, β-CD, and γ-CD were recorded [200]. The effects of the inclusion process on the conformational isomerism and on the hydrogen bond interactions of the guests were studied by monitoring sensitive modes, such as the C=O and CH stretching modes, among others. Overall, the spectral observations suggest that the inclusion in the small α-CD cavity impose structural restrictions on the guest not observed with the larger β-CD and γ-CD. For the 4MeOB molecule, only the most stable form is included in α-CD, whereas for 3CB, the most stable form is completely absent from the α-CD complex. Clear evidence of hydrogen bonding interactions with the carbonyl oxygen atom was observed for the 4MeOB.α-CD complex. In addition, the presence of a C-H...O=C hydrogen bond in the B.α-CD structure is suggested by the changes observed in the region of the CH stretching modes. *Ab initio* calculations were performed for the isolated benzaldehyde molecule, considering both the monomer and the dimer structure occurring in the inclusion complex [201] using the Gaussian 98w program package [202]. Molecular geometries were fully optimized at the standard HF/6-31G* and B3LYP/6-31G* levels [202]. Harmonic vibrational wavenumbers were

computed using analytical second derivatives. The BSSE correction for the dimerization energy was evaluated by counterpoise calculations using the MASSAGE option of G98w.

The properties of inclusion complexes of 1,4-di-R-bicyclo[2.2.2]octanes (R = H **(15)**, Me **(16)**, Cl **(17)**, Br **(18)**, OH **(19)**, Me,OH **(20)**) with CDs have been studied by various NMR-techniques, microcalorimetry and MM and MD computations [203]. Compounds **(16)**, **(17)** and possibly **(18)** (but not the other compounds) gave dynamically stable 1:2 guest-host complexes with α-CD, but did not show any indication of a 1:1 complex. Microcalorimetry of **(19)** in water indicated a moderately strong 1:1 complex with β-CD but at best very weak complexes with α- or γ-CD. The asymmetrically substituted **(20)** behaved similarly to **(19)**. The behavior depends on the subtle interplay of size, polarity, hydrophobicity, type of solvent and temperature. The origin of the unusually high barrier for formation of the 1:2 complex is proposed to be unsynchronized entropy and enthalpy development, originating in the requirement for strong pre-organization in the formation of the complex. A slow exchange between dissolved and dispersed **(16)** was observed and characterized in the solution in the same temperature range. The 1:1 and 1:2 complexes of the compounds **(16)**, **(19)** and **(20)** with α- and β-CD were studied by MM computations using several force fields in Macromodel version 6.5. For the 1:1 α-CD complexes in the gas phase, MC searches using the AMBER force field and allowing for translation and rotation of the guest molecule followed by energy minimization resulted in a stable and unique inclusion complex only for **(16)**. For **(19)** and **(20)** structurally different minima within a few kcal/mol were found, the global minima being externally hydrogen bonded complexes. Using β-CD as host, global minima were 1:1 inclusion complexes with all substrates. In order to achieve more information, the dynamic behavior of the complexation was considered in MD simulations on **(16)**, **(19)**, and **(20)**. This work illustrates that minor structural modifications can totally change affinity, structure and dynamics of binding of related molecules to CDs.

The inclusion compounds formed between β-CD and the tetrafluoroborate salts $[Cp'Mo(\eta^4\text{-}C_6H_8)(CO)_2][BF_4]$ and the neutral derivatives $Cp'Mo(\eta^3\text{-}C_6H_7)(CO)_2$[Cp′= Cp ($\eta^5\text{-}C_5H_5$), Ind ($\eta^5\text{-}C_9H_7$)] were studied by means of elemental analysis, FTIR spectroscopy, thermogravimetric analysis, powder X-ray diffraction, and magic-angle spinning NMR (^{13}C, ^{11}B) [204]. Additional information concerning the possible structure of the inclusion compounds was obtained from *ab initio* calculations using a two-layer approximation. The cationic and neutral η^5-cyclopentadienyl analogues form stable two-to-one (host-to-guest) channel-type inclusion compounds in a crystalline state. By contrast, the η^5-indenyl analogues form only weak complexes with β-CD and it is evident that the organometallic guests are easily liberated from the host cavities. The *ab initio* calculations revealed that the steric hindrance arising from the presence of the indenyl ligand is a possible explanation for the experimentally observed lower stability of these compounds. *Ab initio* calculations for the organometallics were performed using the G98w program package [202] and they yielded molecular structures in agreement with the available X-ray data for similar systems [205]. An interesting feature is revealed by the calculated vibrational spectra: while the observed wavenumbers of the ring ligands are generally well predicted for the organometallics, the calculated scaled wavenumbers

of the carbonyl ligands stretching modes are blue-shifted, approaching the experimental values for the inclusion compounds. The *ab initio* calculations provided valuable insight into the possible inclusion geometries and hence the relative stabilities of the CDs complexes.

Mayer *et al* have investigated the solution structures of the β-CD complexes between 2,3-diaz(o)bicyclo[2.2.2]oct-2-ene **(21)** and its 1-isopropyl-4-methyl derivative **(22)** by means of induced circular dichroism (ICD) and MM3-92 force field calculations, which considered the effect of solvation within a continuum approximation [206]. Of primary interest was the so-called co-conformation of the host-guest complex, *i.e.*, the relative orientation of the guest within the host. A pool of low-energy complex structures, which were located by means of a MC simulated annealing routine, was generated to evaluate the dynamic conformational variability of the complexes. The ICD effects were calculated for the computed low-energy structures by applying a semiempirical method. The experimental and theoretical ICD as well as the calculated low-energy complex geometries suggested solution co-conformations in which the parent compound **(21)** adopts a lateral arrangement with the ethano bridge of the guest penetrating deepest into the cavity and the azo group aligning parallel to the plane of the upper rim. In contrast, the alkyl derivative **(22)** produces a frontal co-conformation with the isopropyl group penetrating deeper into the cavity and the azo group aligning perpendicular to the plane of the upper rim. The validity of the predictions of the Harata rule regarding the sign and the intensity of the ICD signals for the $n_{-}\rightarrow\pi^*$, $n_{+}\rightarrow\pi^*$, and $\pi\rightarrow\pi^*$ transition of the azo chromophore in dependence on the complex co-conformations are discussed. With respect to the co-conformational variability of the complexes of the two azoalkanes, it was observed that the nearly spherical guest **(21)** forms a geometrically better defined complex than the sterically biased, alkyl-substituted derivative **(22)**. This dichotomy is attributed to the largely different modes of binding for azoalkanes **(21)** and **(22)**. It is concluded that the goodness-of-fit in a host-guest complex cannot be directly related to the "tightness-of-fit". The potential energy computations of the 1:1 complexes between the two guest molecules and the host β-CD were performed by using Allinger´s MM3-92 force field and a block diagonal matrix minimization method [64]. Low-energy complex geometries were located by employing a MC simulated annealing routine [207,208] within the program package MultiMize [209]. Both potential energies (calculated by the force field) and solvation effects (calculated by a continuum approximation assigning atomic solvation parameters σ_j to the solvent accessible molecular surface area A_j) were considered within a modified Metropolis criterion, which has been shown to provide a reliable structural data for CDs complexes in aqueous solution [210-212]. Energies and electric moments needed to calculate the rotatory strength for electronic transitions were determined using the semiempirical quantum mechanical method CNDO/S, which is particularly well parametrized for the calculation of electronic transition energies.

Scanning tunneling microscopy has been used to image on a highly orientated pyrolytic graphite substrate an inclusion complex between the sodium salt of the trisulfonated triphenylphosphine (TPPTS) and the β-CD [213]. The images were in good agreement with the structure that has been reported for this inclusion complex and it was postulated that β-CD/TPPTS inclusion complex lies on the apolar graphite substrate by its primary face. A correlation of image contrast with the frontier orbitals of the inclusion

complex is also clearly established for the first time in the case of CD-based supramolecular assemblies. The self-assembly of the inclusion complexes on the graphite surface was also discussed. Two-phenyl groups outside the β-CD cavity dominate the image contrast of the β-CD/TPPTS inclusion complex, and no contribution of the β-CD was observed. Simulations were carried out using CAChe **[214]**. All energy minimizations were performed by using successively steepest descent, conjugate gradient and Newton-Raphson algorithm, with final convergence fixed to 0.001 kcal/mol. Each inclusion mode of TPPTS was investigated by moving the guest along a vector perpendicular to the mean place of the CD linkage oxygen atoms O4, with a 0.2 Å increment. Each structure was fully energy minimized. HOMO and LUMO were realized for the most stable conformation derived from the docking simulation. This calculation was performed by the use of the hamiltonian MNDO, as distributed in SPARTAN [144].

A crystalline 1:1 inclusion complex was isolated from the reaction of β-CD with aqueous Cp_2MoCl_2 [215]. The existence of a true inclusion complex in the solid-state was confirmed by a combination of powder X-ray diffraction, thermogravimetric analysis, FTIR and Raman spectroscopy and magic-angle spinning ^{13}C NMR spectroscopy. *Ab initio* calculations were carried out to generate the possible inclusion geometries and to calculate the vibrational frequencies for Cp_2MoCl_2 in the 100-400 cm^{-1} region. The best organometallic/β-CD interaction geometry was found to be one with one Cp ligand inside the host cavity. The vibrational spectra support the existence of this structure and in addition confirm that the organometallic is included with the Mo-Cl bond intact. *Ab initio* calculations were carried out using the Gaussian98w package [202]. For the free organometallic, the geometry was fully optimized at the B3LYP level using the Dunning/Huzinaga valence double-zeta basis set for the first period elements [216] and the Los Alamos Effective Core Potentials plus doble-zeta [217] for the Mo atom (LanL2DZ option of Gaussian98). Harmonic vibrational frequencies were calculated at the same level, using analytic second derivatives. For comparison with the experimental values, calculated wavenumbers were scaled by a factor of 0.98. In what concerns the inclusion compounds, several possible inclusion geometries were tested by single-point calculations using the two-layer approximation of Morokuma *et al* [218-220] (ONIUM keyword of Gaussian98). The organometallic was treated as high layer, using the effective core potentials described above (B3LYP/LanL2DZ) while the β-CD was set as low layer, and optimized at the HF level with the Stevens/Basch/Krauss Effective Core Potentials minimal basis [221,222].

Steady-state fluorometric studies have been performed on 2-(2′-hydroxyl-5′-methylbenzoyl)-1,5-diphenylpyrrole (HMBDPP) in aqueous and aqueous-β-CD environments at ambient temperature [223]. The fluorophore mostly shows a single emission in aqueous solution. Addition of β-CD to the aqueous solution of the fluorophore results in the development of another emission band at higher energy. The difference in the fluorometric behaviour is assigned to a remarkable change in the polarity of the microenvironment within the supramolecular structural environment compared to that of the bulk aqueous phase. Semi-empirical calculation (AM1-SCI [81]) rules out the possibility of intramolecular proton transfer reaction in any of the S_0, S_1, and T_1 states of the fluorophore. It is proposed that HMBDPP exists mostly in the intermolecular-hydrogen-bonded form (open conformer) in aqueous solution while

within β-CD environment; it is the intramolecular-hydrogen-bonded form (closed conformer) that predominates.

Free energy simulations

Chiellini *et al* carried out a computational study of host-guest inclusion complexes between β-CD and the 20 natural L-α-aminoacids and some selected pentapeptides aimed at understanding the nature of the driving forces and mechanism leading to their formation [224]. Relative complexation energies for the complexes with β-CD were calculated in both cases and the solvation Gibbs free energies were also calculated for the single L-α-aminoacids. The computed results indicated strong possibilities of formation of inclusion complexes between β-CD and single L-α-aminoacids as well as pentapeptides, which have hydrophobic side chains. In addition, noteworthy interactions of the side chain of the pentapeptides with the β-CD were also elucidated. A detailed MD calculation of one of the representative pentapeptide/β-CD inclusion complex (β-CD/CH_3-Ala-Ala-TYR-Ala-Ala-CH_3) in aqueous solution has also been carried out.

MD calculations support aspects connected with the formation and description of hydrogen bonds and with the role of dispersion forces in the inclusion complex in water. All structures of the model L-α-aminoacids (AA), β-CD and β-CD/AA complexes were all modeled using the Insight II molecular modeling package of BIOSYM/MSI [82]. MM calculations for β-CD, model α-aminoacids, and β-CD/AA complexes were carried out using the CVFF and all-atom model, without non-bonding interaction cut-off, employing the Discover package of BIOSYM/MSI [154]. To analyze in detail the nature of interactions of β-CD with the backbone of polypeptides, a similar set of calculations was performed for the complexes of the same L-α-aminoacid side chains located at the center of a symmetrical pentapeptide constituted on both sides by two alanine (Ala) residues. The Ala residues at the terminal N- and C- ends were arbitrarily capped with two methyl groups. The solvation Gibbs free energies were calculated using the Polarizable Continuum Model [86,225]. Here the solute is represented by a set of point atomic charges derived from the CVFF force field and it is placed in a cavity of realistic shape composed of intersecting spheres with van der Waals radii centered on individual atoms. The solvent is represented by a homogeneous dielectric medium of permittivity $\varepsilon = 80$ (water). MD calculation of one of the representative system of the guest-host complex has been carried out for the β-CD/CH3-Ala-Ala-TYR-Ala-Ala-CH3 complex in water (184 water molecules in a cubic box of size 20 A) for 500 ps at room temperature.

Luzhkov and Aqvist have examined the use of free-energy perturbation simulations for calculating binding and transition-state energies [226]. Reactions of three phenyl esters with β-CD were considered. The binding free energies were calculated using conventional mutation of the substrate force field from one chemical structure to another (two-state problem) in water and in the neutral inclusion complex. For calculating the activation free energy differences between two substrates, the transition states were represented by linear combinations of reactant (anionic inclusion complexes) and product (tetrahedral intermediate) force fields (four-state problem). The coefficients of this linear combination were obtained from empirical valence bond (EVB) simulations of a reference substrate. The calculated relative binding and activation energies were in

good agreement with available experimental data. All calculations were carried out with the MD program Q [227]. The GROMOS87 potential energy function [228] was used together with calibrated EVB parameters [229]. In this work authors have addressed the issue of substrate specificity by calculations where the ligand structures are mutated in solution, in the reactive complex and in the transition state of the reaction.

The λ-dynamics approach to free energy simulations has been applied to the host-guest system of β-CD interacting with a series of mono-substituted benzenes [230]. Each ligand was explicitly represented, and restraining potentials [231] were used to hold back the unselected ligands in nearly binding conformations. Using biasing potentials to enhance convergence, excellent correlation between the free energies derived from λ-dynamics and free energy perturbation results were obtained. Effects of the strength of the restraining potentials and bias potentials on the sampling of the conformational space have been examined. Ligands with smaller substituents explored alternate binding orientations in the presence of weak and moderate restraining potentials. MD has been used to sample both the λ- and conformational spaces in the implementation of this approach, called λ-dynamics [232]. This method has been applied to the screening of ligands using both hybrid topology and multiple topology representations with excellent results [233]. Modeling the ligands using a multiple topology representation results in an enhanced sampling of the conformational space and potentially rapid convergence because the ligands weakly coupled to the environment ($\lambda \approx 0$) are not constrained to the binding orientation of the dominant ligand as in a hybrid model. However, this may lead to slower convergence, since decoupled ligands "wander away" from the bonding site and do not return during the finite simulation time. To overcome this problem, Banba and Brooks added a restraining potential to the hamiltonian [231]. The effect of the restraining potential is corrected for while calculating the free energies. The reliability of this method has also been demonstrated by using this approach to screen a set of ligands binding to an artificial cavity in cytochrome-C peroxidase. Excellent correlation was obtained between free energies calculated from FEP simulations and λ-dynamics [231].

Enantiomers separation

Circular dichroism is an essential spectral property for probing chirality [234,235]. An interesting effect arises when an achiral guest chromophore is complexed in a chiral host. The guest becomes optically active, a phenomenon referred to as "induced" circular dichroism (ICD) [26, 236, 237]. The spectroscopic information resulting from this interaction is unique, since sign and magnitude of the ICD signal depend on the relative orientation of the chromophore in the host. Harata *et al* have developed a rule for the inclusion complexes of cone-shaped chiral hosts like CDs [238]. According to this rule, a positive ICD signal arises when the electric transition dipole moment is aligned parallel to the axis of the host, but the signal is negative and half as strong when it is oriented in a perpendicular manner [235,237]. More recently, a similar rule has also been developed for ICD effects outside the host cavity [162], where the sign of the ICD signal is opposite to that arising inside the host cavity, and a refined computational treatment for ICD effects has been introduced [239,240]. Knowledge of the relative orientation of the guest in host-guest complexes, in particular when weak van

der Waals interactions operate [236], is important for the development of functional supramolecular materials, such as those for catalytic or analytical purposes.

Zhang and Nau [241] have provided an example for a conformational assignment of host-guest complexes in solution. The ICD effects, predicted by Harata´s rule, were observed for azoalkanes and azoalkanes sterically modified, for which two different modes of inclusion in a CD apply. These results are a sensitive test case for Harata´s rule, since the transition moment of the localized azo chromophore is insensitive to the alkyl substitution pattern. This "structural test" is distinct, compared to earlier studies [163, 238, 242-244], since a whole chromophore is actually flipped around in the chiral cavity. Further insight into the specific modes of inclusion in β-CD was obtained by force-field calculations [185]. AMBER [160] computations produced four principal conformations of azoalkanes in β-CD. Simulations using MD [245] retained the four principal conformations.

The intermolecular forces responsible for complexation of equol, a chiral molecule, with β-CD were determined using a molecular modeling study [246]. The differential interactions between each enantiomer and the chiral host give rise to different configurations for the corresponding inclusion complexes, which give rise to enantio-differentiation. The van der Waals term is the main contributor to the total potential. However, the electrostatic term influences the enantio-selectivity significantly since it establishes a difference between the most stable position of R- and S-equol and hence between their energies. A statistical analysis of the minimized energies was carried out to determine that R-equol is more retained than S-equol. The geometries of both enantiomers of equol were calculated using the AM1 semi-empirical hamiltonian [81] included in the MOPAC 6.0 package [247]. In all cases, the presence of minima was confirmed by inspection of the hessian. The lowest-energy configuration of host-guest complexes formed by CD with both enantiomers was determined assuming that inclusion complex formation does not affect the structure of either molecule, keeping the internal coordinates of both guest and host fixed. In this work the molecules were described by the all-atom model as this offers a somewhat better description of the potential surfaces. The intermolecular energy was represented by contributions from van der Waals, hydrogen bonding and electrostatic functions, as in AMBER force field [140,141].

^{1}H and ^{13}C NMR spectra of the complexes of camphor enantiomers with α-CD in D_2O manifest splittings due to chiral recognition. The complexes were found to be of 1:2, guest-to-host, stoichiometry [248]. Free energies of the complex formation obtained from ^{1}H NMR titration data were equal to –7.95 ±0.09 kcal/mol for the complex with (1*S*, 4*S*)- and –7.61 ±0.06 kcal/mol for that with (1*R*, 4*R*)-enantiomer. Thus, the free energy difference between the complexes is equal to 0.34 ±0.11 kcal/mol, with the complex involving the (1*S*, 4*S*)-camphor more stable. A strong cooperativeness of the guests binding has been found. In agreement with experimental results, MD simulations yielded greater stability of the complex with (1*S*, 4*S*)-camphor. However, they reproduced only qualitatively the experimental trend since the corresponding difference in average energies obtained from MD simulations carried out in water solution is equal to 5 kcal/mol with the CVFF force field. The calculations were performed using the Insight II program [249] with the CVFF force field [84]. MD simulations were carried out in a vacuum at 300 K for 1:1 complexes with both enantiomers and showed that the

complexes decomposed after about 10 ps. Contrary to that, MD runs for all 1:2 camphor-CD dimeric complexes studied both in vacuum and in water boxes demonstrated extreme stabilities of the molecular ensembles on the nanosecond time scale. Authors concluded that MD simulations in solvent with relatively long simulation times reproduce only qualitatively the experimental trend.

Chiral recognition of α-amino acid derivatives by charged β-CDs has been studied by means of ^{1}H NMR spectroscopy [250]. Protonated heptakis(6-amino-6-deoxy)-β-CD (per-NH_3^+-β-CD) forms complexes with the (*S*)-enantiomers of *N*-acetylated Trp, Phe, Leu and Val in their anionic forms more preferentially than the (*R*)-enantiomers, though the difference in the binding constants (K) between the enantiomers is small. Inclusion of the guest into the host cavity and intermolecular Coulomb interactions participate cooperatively in complexation. Monoaminated β-CD (mono-NH_3^+-β-CD) also recognizes the chirality of the amino acids while native CDs such as α- and β-CDs do not. The K values for the per-NH_3^+-β-CD-guest anion complexes are much larger than those for the mono-NH_3^+-β-CD complexes.

The large K value of the per-NH_3^+-β-CD-(*S*)-AcTro complex is ascribed to a large positive ΔS value which might be due to extended dehydration of both host and guest during complexation. The enantio-selective complexation was also found in the system composed of the α-amino acid methyl esters in the cationic forms and heptakis[6-(2-thioglycolic acid)-6-deoxy]-β-CD in the anionic form where the (*R*)-enantiomers were preferable guests. Standard MM and MD calculations including the effects of water were made [251] and they demonstrated the advantage of Coulomb interactions as an attractive force in the recognition of central chirality in the host-guest chemistry.

Chiral recognition of mandelic acid **(23)**, acetylmandelic acid **(24)**, 1-methoxyphenylacetic acid **(25)**, phenylsuccinic acid **(26)**, 2-phenylpropanoic acid **(27)**, and ibuprofen **(28)** in their anionic forms by protonated 6^A-amino-6^A-deoxy-β-CD (mono-NH_3^+-β-CD) and 6^A,6^D-diamino-6^A,6^D-dideoxy-βCD (di-NH_3^+-β-CD) has been studied by means of capillary zone electrophoresis (CZE) and ^{1}H NMR spectroscopy [252]. Both methods show the preferable guests for mono-NH_3^+-β-CD to be the (*R*)-enantiomers of **(23)**, **(25)** and **(27)** and the (*S*)-enantiomers of **(24)**, **(26)** and **(28)**. Cooperative work of Coulomb interactions and inclusion is essential for chiral recognition of these anionic guests. MM and MD calculations were performed by the use of the AMBER program system (Version 4) [160] at 250-300 K for 12 ps (time step 0.001 ps). The effects of water molecules as solvent were involved. The data on charges were collected using a MOPAC program (Version 6) [91].

When β-CD interacts with the enantiomers of a chiral molecule, the difference in chiral properties between host and guest affects the host-guest interaction and the stability of the inclusion, giving rise to chiral discrimination [253-256]. In addition, different degrees of fit between the guest enantiomers and the host may influence the degree of hydration of the inclusion system. Since enantiomers undergo identical solvation processes, the study of the host-guest interactions between β-CD and the enantiomers of a chiral molecule should provide a better insight into these interactions and elucidate chiral recognition processes in biological receptor molecules. Two enantiomers of carvone (2-methyl-5-(1-methylethenyl)-2-cyclohexene-1-one, Crv) are natural components of spearmint [(R)-(-)-carvone, R-Crv] and caraway seed oil [(S)-(+)-

carvone, S-Crv]- As a hydrogen bond acceptor, the C=O bond of carvone can act as the anchoring group for the guest in the inclusion process, a possibility which can determine the preferencial fixation of one of the enantiomers [255,256]. TeixeiraDias *et al* [257] have studied the apparent association constants for the inclusion of the carvone enantiomers in β-CD in D_2O solution, at different temperatures, by ^1H NMR. In addition, MM and quantum mechanics calculations on model systems were carried out to help in the interpretation of the experimental results. Semi-empirical and *ab initio* calculations were performed on four model systems: in two of the models (S-*up*, R-*up*), the C=O bonds of the carvone enantiomers were closer to the wider β-CD rim (*up*-orientation), whereas, in the other two (S-*dn*, R-*dn*), the C=O bonds of the carvone enantiomers were closer to the narrower β-CD rim (*down*-orientation). MM results were generated using the program Cerius^{2TM} with the Dreiding force field [258]. Quantum mechanics calculations were carried out for β-CD and carvone molecules, as well as for model systems of the inclusion compounds, using the Gaussian Program for Windows, G94W [185]. Computations were made at the semiempirical (AM1 method) and STO-3G basis set levels. Both calculations confirmed S-*dn* as the more stable model system, in consonance with both the MM results and with the experimental data, which indicated a preferential inclusion of the S.Crv enantiomer. In addition, the quantum mechanical calculations revealed the importance of multiple CH...O(=) interactions of the hydrogen bonding type for the relative stability of the model systems therein considered. This result was in consonance with the reduction of the relative stability of β-CD/S-Crv as the temperature increases.

Kano and Hasegawa [259] have reported results on the recognition of chirality of metal complexes $M(phen)_3^{n+}$ (M = Ru(II), Rh(III), Fe(II), Co(II), and Zn(II), and phen = 1,10-phenanthroline) by heptakis(6-carboxymethylthio-6-deoxy)-β-CD heptaanion (per-CO_2^--β-CD) and hexakis(2,3,6-tri-*O*-methyl)-α-CD (TMe-α-CD) in D_2O. The binding constant (K) for the Δ-$Ru(Phen)_3^{2+}$ complex of per-CO_2^--β-CD in 0.067 M phosphate buffer at pD 7.0 is ~2 times larger than that for the Λ-isomer. Definite effects of inorganic salts on stability of the complexes indicate a large contribution of Coulomb interactions to complexation. The fact that hydrophilic $Ru(bpy)_3^{2+}$ (bpy = 2,2′-bipyridine) does not form a complex with per-CO_2^--β-CD suggests the importance of inclusion of the guest molecule into the host cavity for forming a stable ion-association complex. The positive entropy change for complexation of $Ru(phen)_3^{2+}$ with per-CO_2^--β-CD shows that dehydration from both the host and the guest occurs upon complexation. Similar results were obtained with trivalent $Rh(phen)_3^{3+}$ cation. Pfeiffer effects were observed in complexation of racemic $Fe(phen)_3^{2+}$, $Co(phen)_3^{2+}$, and $Zn(phen)_3^{2+}$ with per-CO_2^--β-CD with enriched Δ-isomers. Native CDs such as α-, β-, and γ-CD as well as heptakis(2,3,6-tri-*O*-methyl)-β-CD do not interact with $Ru(bpy)_3^{2+}$. However, hexakis(2,3,6-tri-*O*-methyl)-α-CD (TMe-α-CD) interacts with $Ru(phen)_3^{2+}$ and $Ru(bpy)_3^{2+}$ and discriminates between the enantiomers of these metal complexes. The K values for the Δ- and Λ-$Ru(phen)_3^{2+}$ ions are 54 and 108 M^{-1}, respectively. Complexation of the Δ- and Λ-isomers of $Ru(phen)_3^{2+}$ with TMe-α-CD is accompanied by negative entropy changes, suggesting that cationic $Ru(phen)_3^{2+}$ is shallowly included into the cavity of the neutral host through van der Waals interactions. The Δ-enantiomers, having

a right-handed helix configuration, fits the primary OH group side of per-CO_2^--β-CD ($SCH_2CO_2^-$ side) well, while the Λ-enantiomer, having a left-handed helix configuration, is preferably bound to the secondary OH group side of TMe-α-CD. The asymmetrical twisted shape of a host cavity seems to be the origin of chiral recognition by CD.

The energy-minimized structure of per-CO_2^--βCD was obtained from the MD calculation using a HyperChem® program [98], which corresponds to AMBER version 3a [160]. The calculation was carried out by setting the initial and final temperatures at 250 and 298 K, respectively, the heat time of 1 fs, and the run time of 100 ps. Four hundred and two water molecules were placed in a box in which a per-CO_2^--β-CD ion was located.

Quantitative structure-activity (property) relationships

Owing to its more favorable complexing ability and lower price, β-CD is the most common CD, largely used as solubilizing and stabilizing agent in pharmaceuticals, food and cosmetics. In environmental technology β-CD and derivatives are proposed for detoxification of industrial wastewaters and remediation of hazardous waste sites [5]. To establish mathematical models that relate activity to the structure in a series of compounds is useful for predicting the behavior of additional untested compounds of the series. Carpignano *et al* have reported a quantitative structure-activity relationships (QSAR) study of the complexation of a series of non-substituted heterocyclic compounds with β-CD [260]. A training set of compounds was selected among eighteen commercially available heterocycles by a multivariate statistical design. The measured stability constants of the complexes were modeled as a function of the heterocycle structure by Partial Least Squares (PLS) [261] method and the model developed was used to predict the stability constants of other compounds of the series. They showed that separate models for heterocyclic compounds containing nitrogen, alone or with a second heteroatom, and for compounds with oxygen or sulfur in the ring, are needed in order to have a satisfactory predictive ability. The variation in the structure of the heterocycles was described by global molecule properties (physicochemical and spectroscopic properties) and indicator variables. The physicochemical properties selected were melting point, boiling point, enthalpy of formation, enthalpy of combustion, dipole moment and log P, factors known to influence the stability of CD complexes, like polarity, hydrophobicity and cohesive forces between guest molecules. The spectroscopic properties are ^{13}C NMR chemical shifts of carbons of the benzene ring present in all the heterocyclic compounds. Analysis of numerical data allowed to demonstrate that the presence of S in the heterocyclic rings results in a considerable increase of the stability of the complex while the effect is lower for O heteroatom and the presence of N, alone or with a second heteroatom, decreases strongly the complex stability. Besides, di-benzo heterocyclic compounds show higher stability than mono-benzoderivatives.

Suzuki developed a group-contribution method for calculating the binding constants or the free energies of complexation between native α- or β-CD and organic guest molecules [262]. The nonlinear models for binary (1:1 stoichiometry) complexes of α- and β-CDs were derived with squared correlation coefficients (r^2) of 0.868 and 0.917 based on a database consisting of 102 and 218 diverse guest molecules, respectively. The parameters used in the models are first-order molecular connectivity index as a measure

of molecular bulk and atom/group counts in the guest molecules. The models allowed accurate estimations for the wide range of guests containing C, H, N, O, S, and/or all halogens by summing the contribution values of each defined group present in the chemical structure of the guest along with guest's molecular size factors (linear and square terms) and then the summation to a constant coefficient value. The predictive performance of the models was tested with 27 extra compounds not included in the original data set. The predicted values by the models were in good agreement with the experimentally determined data. Suzuki concluded that group-contribution models for the estimation of the thermodynamic stability of the complexation of a large variety of organic compounds with natural α- and β-CDs, respectively, were established. His results demonstrated that a single set of chemical substructures and the descriptor incorporating molecular size, first-order molecular connectivity index; allow an accurate prediction of the free energies of complexation. The models proposed in this work provide a basis for the evaluation of the reliability of the experimentally determined data as well as the prediction for the complexation properties of guest molecules for which the experimental determination is difficult or exceedingly time-consuming.

Quantitative models were found to describe the complexation of α- and β-CD with mono- and 1,4-disubstituted benzene derivatives by using combinations of 2D-, 3D-connectivity and quantum chemical molecular descriptors [263]. The association constants (K_a) for the inclusion complexation of CDs and benzene derivatives are calculated by models found with a high degree of precision. These models also permit the interpretation of the driving forces of such complexation processes. In the case of the complexation of α-CD with benzene derivatives these driving forces are mainly the electronic repulsion between frontier orbitals (HOMO and LUMO, respectively) of the host and guest molecules. However, the complexation of β-CD with benzene derivatives is controlled by topological and topographic parameters indicating the relevance of the van der Waals and hydrophobic interactions. The authors also carried out molecular modeling studies showing that for α-CD complexes the benzene rings remain outside the cavity of the CD, while in β-CD they penetrate deeply into the apolar and hydrophobic cavity of the host, which explains the differences in the driving forces for both complexation processes.

Two data sets of benzene derivatives were studied in this work. The first data set is formed by 56 mono- and 1,4-disubstituted benzenes for which the K_a's for the inclusion complexation with α-CD were determined experimentally and further compiled by Liu and Guo [264]. The second data set is formed by the K_a's for the inclusion of 46 mono- and 1,4-disubstituted benzene derivatives with β-CD [264]. 2D vertex and edge molecular connectivity indices of different types and orders were calculated by the computer system MODEST for Windows [265]. In computing 3D connectivity indices full geometry optimization of the benzene derivative structures was carried out by the semiempirical quantum chemical method AM1 [81]. Then the output files were used as input for the system MODEST in order to compute the topological, topographical, and quantum chemical descriptors. The full geometry optimization calculations were done with MOPAC 6.0 [91] by using the keyword PRECISE in order to obtain better precision. Two other keywords used were VECTORS to generate the eigenvectors of the wave function and the word BONDS to obtain the bond orders and valences of the

correspondent bonds and atoms in the molecules, which are employed in the definition of 3D connectivity indices. MM calculations of the complexation of α- and β-CD with some benzene derivatives were carried out using the MM2 force field and full-geometry optimization with the Hyperchem® software [152]. The molecules of the guest were introduced into the host according to two possible orientations, and the minimum energy was determined in both cases. These orientations were (a) introducing the substituent through the widest cavity of the CD, or (b) introducing the phenyl ring through the widest cavity of the CD. In all cases the orientation (a) resulted the most stable. These models using such combination of molecular descriptors resulted better than any other known models using only one type of the studied descriptors. The authors found that the main driving force for the complexation of α-CD with benzene derivatives are the electronic repulsions, mainly between frontier orbitals, of the host and guest molecules. The other factors, van der Waals and hydrophobic interactions, are mainly non-significant in this complexation. It is due to this fact that the benzene derivatives do not penetrate into the cavity of the CD, as has been proved by their molecular modeling calculations. On the contrary, the complexation process of β-CD with benzene derivatives is controlled by topological and topographic parameters indicating the relevance of the van der Waals and hydrophobic interactions that are mainly dependent on such structural features. These interactions are the main cause for the deep penetration of benzene derivatives into the cavity of the CD that is mainly apolar and hydrophobic. In this case the electronic interaction is not a driving force of the process of complexation as it is proved by the lack of any quantum chemical descriptor in the QSPR model.

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